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Synthesis of novel alkaloids using squaric acid esters

Peter S. Zehr
West Virginia University

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Synthesis of Novel Alkaloids Using Squaric Acid Esters

Peter S. Zehr

Dissertation submitted to the Eberly College of Arts and Sciences
at West Virginia University
in partial fulfillment of the requirements for
the degree of

Doctor of Philosophy
in
Organic Chemistry

Björn C. Söderberg, Ph.D., Chair
John H. Penn, Ph.D.
Alan M. Stolzenberg, Ph.D.
Kung K. Wang, Ph.D.
Peter M. Gannett, Ph.D.

Department of Chemistry

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cyclopenta[*b*]quinolines

Abstract

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Peter S. Zehr

A novel route to cyclopenta[*b*]quinoline-1-ones and –ols has been developed. Substituted cyclopenta[*b*]quinolin-1-ones were prepared by thermal ring-expansion of substituted *N*-BOC protected 4-(2-aminophenylethynyl)-4-hydroxy-2-cyclobuten-1-ones forming the corresponding 2-aminophenylmethylidene substituted 4-cyclopentene-1,3-diones. Deprotection of the amine resulted in spontaneous condensation to give cyclopenta[*b*]quinolin-1-ones. Sodium borohydride reduction of these products produced cyclopenta[*b*]quinolin-1-ols. The key step in the sequence is a thermally induced ring-expansion of 4-(2-aminophenylethynyl)-4-hydroxy-2-cyclobuten-1-ones. Changing the amino protecting group had no effect on the ring size selectivity of the thermal ring expansion. The thermal ring expansion of the corresponding nitro derivative suggests that electron withdrawing substituents may alter the selectivity of the ring formation. The attempted base mediated, copper mediated, copper catalyzed and palladium catalyzed indolization reaction were not further examined since the desired products were not obtained. The *N*-iodosuccinimide, *N*-chlorosuccinimide mediated and palladium catalyzed ring expansion reactions were also not further examined. The copper acetate catalyzed indolization of the *N*-acetyl derivative may lead to the preparation of novel 2-substituted indoles. In the CuI mediated reactions with *N*-benzyl the project was dropped since the starting material was difficult to synthesize. A novel route to indoloquinones has been developed. This methodology may lead to the synthesis of a natural product, as well as several novel indoloquinones.

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Table of Contents

Title page	i
Abstract.....	ii
Acknowledgments.....	iii
Table of Contents.....	iv
List of Figures	vii
List of Schemes	xv
List of Tables	xvii

Part I

A Novel Entry to Cyclopenta[*b*]quinolines *via* Thermal Ring- Expansion of (2-Aminophenyl)-Ethynyl-Substituted Cyclobutenone Derivatives

1. Introduction	1
a. 1.1. Quinoline Syntheses: Intramolecular Cyclization of Anilines	2
b. 1.2. Quinoline Syntheses: Cyclization of Ortho-Disubstituted Benzenes	5
c. 1.3. Modern Quinoline Syntheses	7
d. 1.4. Cyclobutenediones.....	8
2. Results and Discussion.....	11
a. 2.1. N-BOC Protected Derivatives.....	12
b. 2.2. <i>N</i> -Acetyl and <i>N</i> -benzyl aniline	27

c. 2.3. Nitrobenzene Derivative	31
3. Conclusions	32

Part II

Attempted Indolizations and Additional Ring Expansions

1. Introduction	34
a. 1.1. Indolization Methods	35
b. 1.2. Electrophilic Ring Expansions 4-Hydroxy-2-cyclobuten-1-ones	38
2. Results and Discussion.....	40
a. 2.1. Base Mediated Indole Formation	41
b. 2.2. Attempted Copper Mediated Indole Formation.....	42
c. 2.3. Copper Acetate Catalyzed Indole Formation.....	44
d. 2.4. Attempted Palladium Catalyzed Indole Formation or Ring Expansions.....	45
e. 2.5. <i>N</i> -Iodosuccinimide Mediated Ring Expansion	45
f. 2.6. <i>N</i> -Chlorosuccinimide Mediated Ring Expansion	46
3. Conclusions	48

Part III

Synthesis of Novel Indoloquinones

1. Introduction	49
2. Results and Discussion.....	52
3. Conclusions	58

Part IV

Experimental Section

1. General Procedures	59
2. Experimental Details	60
3. References.....	97
4. Appendix	102

List of Figures

Figure 1: Biologically Active Quinoline	1
Figure 2: Gradient Heteronuclear Multiple Quantum Coherence Spectrum of 35	16
Figure 3: Gradient Heteronuclear Multiple Bond Coherence Spectrum of 35	17
Figure 3A: Indoloquinone Containing Natural Products	49
Figure 4: ^1H Spectrum of (4-Chloro-2-iodophenyl)-carbamic acid 1,1-dimethylethyl ester 37b	103
Figure 5: ^{13}C Spectrum of (4-Chloro-2-iodophenyl)-carbamic acid 1,1-dimethylethyl ester 37b	104
Figure 6: ^1H Spectrum of (2-Iodo-5-methoxy-phenyl)-carbamic acid 1,1-dimethylethyl ester 37c	105
Figure 7: ^{13}C Spectrum of (2-Iodo-5-methoxy-phenyl)-carbamic acid 1,1-dimethylethyl ester 37c	106
Figure 8: ^1H Spectrum of (2-Iodo-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester 37d	107
Figure 9: ^{13}C Spectrum of (2-Iodo-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester 37d	108
Figure 10: ^1H Spectrum of (4-Chloro-2-(trimethylsilylethynyl)phenyl)-carbamic acid 1,1-dimethylethyl ester 38b	109
Figure 11: ^{13}C Spectrum of (4-Chloro-2-(trimethylsilylethynyl)phenyl)-carbamic acid 1,1-dimethylethyl ester 38b	110
Figure 12: ^1H Spectrum of (5-Methoxy-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 38c	111
Figure 13: ^{13}C Spectrum of (5-Methoxy-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 38c	112
Figure 14: ^1H Spectrum of (5-Methyl-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 38d	113

Figure 15: ^{13}C Spectrum of (5-Methyl-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 38d	114
Figure 16: ^1H Spectrum of (4-trimethylsilylethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester 38e	115
Figure 17: ^{13}C Spectrum of (4-trimethylsilylethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester 38e	116
Figure 18: ^1H Spectrum of (4-Chloro-2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 26b	117
Figure 19: ^{13}C Spectrum of (4-Chloro-2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester 26b	118
Figure 20: ^1H Spectrum of (2-Ethynyl-5-methoxyphenyl)-carbamic acid 1,1-dimethylethyl ester 26c	119
Figure 21: ^{13}C Spectrum of (2-Ethynyl-5-methoxyphenyl)-carbamic acid 1,1-dimethylethyl ester 26c	120
Figure 22: ^1H Spectrum of (2-Ethynyl-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester 26d	121
Figure 23: ^{13}C Spectrum of (2-Ethynyl-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester 26d	122
Figure 24: ^1H Spectrum of (4-Ethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester 26e	123
Figure 25: ^{13}C Spectrum of (4-Ethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester 26e	124
Figure 26: ^1H Spectrum of [2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 28a	125
Figure 27: ^{13}C Spectrum of [2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 28a	126
Figure 28: ^1H Spectrum of [4-Chloro-2-(1-hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 28b	127
Figure 29: ^{13}C Spectrum of [4-Chloro-2-(1-hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 28b	128

Figure 30: ^1H Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester **28c** and butyl addition product of diisopropyl squarate 129

Figure 31: ^{13}C Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester **28c** and butyl addition product of diisopropyl squarate 130

Figure 32: ^1H Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester **28c** ... 131

Figure 33: ^{13}C Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester **28c** ... 132

Figure 34: ^1H Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methylphenyl]-carbamic acid 1,1-dimethylethyl ester **28d** 133

Figure 35: ^{13}C Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methylphenyl]-carbamic acid 1,1-dimethylethyl ester **28d** 134

Figure 36: ^1H Spectrum of [4-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-pyridin-3-yl]-carbamic acid 1,1-dimethylethyl ester **28e** 135

Figure 37: ^{13}C Spectrum of [4-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-pyridin-3-yl]-carbamic acid 1,1-dimethylethyl ester **28e** 136

Figure 38: ^1H Spectrum of [2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester **33a** 137

Figure 39: ^{13}C Spectrum of [2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester **33a** 138

Figure 40: ^1H Spectrum of [4-Chloro-2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester **33b** 139

Figure 41: ^{13}C Spectrum of [4-Chloro-2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester **33b** 140

Figure 42: ^1H Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-5-methoxy-phenyl]-carbamic acid 1,1-dimethylethyl ester **33c** 141

Figure 43: ^{13}C Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-5-methoxy-phenyl]-carbamic acid 1,1-dimethylethyl ester **33c** 142

Figure 44: ^1H Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-methylidene)-5-methyl-phenyl]-carbamic acid 1,1-dimethylethyl ester **33d** 143

Figure 45: ^{13}C Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-methylidene)-5-methyl-phenyl]-carbamic acid 1,1-dimethylethyl ester **33d** ... 144

Figure 46: ^1H Spectrum of [4-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-3-pyridinyl]-carbamic acid 1,1-dimethylethyl ester **33e** 145

Figure 47: ^{13}C Spectrum of [4-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-3-pyridinyl]-carbamic acid 1,1-dimethylethyl ester **33e** 146

Figure 48: ^1H Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[*b*]quinolin-1-one **34a** 147

Figure 49: ^{13}C Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[*b*]quinolin-1-one **34a** 148

Figure 50: ^1H Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[*b*]quinolin-1-one **34b** 149

Figure 51: ^{13}C Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[*b*]quinolin-1-one **34b** 150

Figure 52: ^1H Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[*b*]quinolin-1-one **34c** 151

Figure 53: ^{13}C Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[*b*]quinolin-1-one **34c** 152

Figure 54: ^1H Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[*b*]quinolin-1-one **34d** 153

Figure 55: ^{13}C Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[*b*]quinolin-1-one **34d** 154

Figure 56: ^1H Spectrum of 2,3-Di(1-methylethoxy)-6-aza-cyclopenta[*b*]quinolin-1-one **34e** 155

Figure 57: ^{13}C Spectrum of 2,3-Di(1-methylethoxy)-6-aza-cyclopenta[*b*]quinolin-1-one **34e** 156

Figure 58: ^1H Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[*b*]quinolin-1-ol **35a** 157

Figure 59: ^{13}C Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[<i>b</i>]quinolin-1-ol 35a	158
Figure 60: ^1H Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[<i>b</i>]quinolin-1-ol 35b	159
Figure 61: ^{13}C Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[<i>b</i>]quinolin-1-ol 35b	160
Figure 62: ^1H Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[<i>b</i>]quinolin-1-ol 35c	161
Figure 63: ^{13}C Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[<i>b</i>]quinolin-1-ol 35c	162
Figure 64: ^1H Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[<i>b</i>]quinolin-1-ol 35d	163
Figure 65: ^{13}C Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[<i>b</i>]quinolin-1-ol 35d	164
Figure 66: ^1H Spectrum of 2,3-Di(1-methylethoxy)-6-azacyclopenta[<i>b</i>]quinolin-1-ol 35e	165
Figure 67: ^{13}C Spectrum of 2,3-Di(1-methylethoxy)-6-azacyclopenta[<i>b</i>]quinolin-1-ol 35e	166
Figure 68: ^1H Spectrum of [2-(1-Hydroxy-2-(1-methylethoxy)-3-methyl-4-oxo-cyclobut-2-enylethynyl)-phenyl]-carbamic acid 1,1-dimethylethyl ester 41	167
Figure 69: ^{13}C Spectrum of [2-(1-Hydroxy-2-(1-methylethoxy)-3-methyl-4-oxo-cyclobut-2-enylethynyl)-phenyl]-carbamic acid 1,1-dimethylethyl ester 41	168
Figure 70: ^1H Spectrum of E- and Z-[2-(3-(1-methylethoxy)-4-methyl-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 42	169
Figure 71: ^{13}C Spectrum of E- and Z-[2-(3-(1-methylethoxy)-4-methyl-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester 42	170
Figure 72: ^1H Spectrum of 2-(1-Methylethoxy)-3-methylcyclopenta[<i>b</i>]quinolin-1-one 43	171
Figure 73: ^{13}C Spectrum of 2-(1-Methylethoxy)-3-methylcyclopenta[<i>b</i>]quinolin-1-one 43	172

Figure 74: ^1H Spectrum of 2-(1-methylethoxy)-3-methylcyclopenta[<i>b</i>]quinolin-1-ol 44	173
Figure 75: ^{13}C Spectrum of 2-(1-methylethoxy)-3-methylcyclopenta[<i>b</i>]quinolin-1-ol 44	174
Figure 76: ^1H Spectrum of N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide 46	175
Figure 77: ^{13}C Spectrum of N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide 46	176
Figure 78: ^1H Spectrum of N-[2-(3,4-Diisopropoxy-2,5-dioxo-cyclopent-3-enylidenemethyl)-phenyl]-acetamide 51	177
Figure 79: ^{13}C Spectrum of N-[2-(3,4-Diisopropoxy-2,5-dioxo-cyclopent-3-enylidenemethyl)-phenyl]-acetamide 51	178
Figure 80: ^1H Spectrum of 3-(1-Acetyl-1H-indol-3-yl)-4-isopropoxy-cyclobut-3-ene-1,2-dione. 70	179
Figure 81: ^{13}C Spectrum of 3-(1-Acetyl-1H-indol-3-yl)-4-isopropoxy-cyclobut-3-ene-1,2-dione. 70	180
Figure 82: ^1H Spectrum of N-[2-(2-Isopropoxy-3,4-dioxo-cyclobut-1-enylethynyl)-phenyl]-acetamide 71	181
Figure 83: ^{13}C Spectrum of N-[2-(2-Isopropoxy-3,4-dioxo-cyclobut-1-enylethynyl)-phenyl]-acetamide 71	182
Figure 84: ^1H Spectrum of <i>tert</i> -butyl 2-(2-(2-isopropoxy-3,4-dioxocyclobut-1-enyl)ethynyl)phenylcarbamate 72	183
Figure 85: ^{13}C Spectrum of <i>tert</i> -butyl 2-(2-(2-isopropoxy-3,4-dioxocyclobut-1-enyl)ethynyl)phenylcarbamate 72	184
Figure 86: ^1H Spectrum of 4-(2-Benzylamino-phenylethynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone 48	185
Figure 87: ^{13}C Spectrum of 4-(2-Benzylamino-phenylethynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone 48	186
Figure 88: ^1H Spectrum of 9-Benzyl-2,3-diisopropoxy-9 <i>H</i> -carbazole-1,4-dione 69	187

Figure 89: ^{13}C Spectrum of 9-Benzyl-2,3-diisopropoxy-9 <i>H</i> -carbazole-1,4-dione 69	188
Figure 90: ^1H Spectrum of 4-(4-Benzylamino-but-1-ynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone 88	189
Figure 91: ^{13}C Spectrum of 4-(4-Benzylamino-but-1-ynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone 88	190
Figure 92: ^1H Spectrum of 1-Benzyl-5,6-diisopropoxy-2,3-dihydro-1 <i>H</i> -indole-4,7-dione 91	191
Figure 93: ^{13}C Spectrum of 1-Benzyl-5,6-diisopropoxy-2,3-dihydro-1 <i>H</i> -indole-4,7-dione 91	192
Figure 94: ^1H Spectrum of 5,6-Diisopropoxy-2,3-dihydro-1 <i>H</i> -indole-4,7-dione 93	193
Figure 95: ^{13}C Spectrum of 5,6-Diisopropoxy-2,3-dihydro-1 <i>H</i> -indole-4,7-dione 93	194
Figure 96: ^1H Spectrum of 1-Benzyl-5,6-diisopropoxy-1 <i>H</i> -indole-4,7-dione 94	195
Figure 97: ^{13}C Spectrum of 1-Benzyl-5,6-diisopropoxy-1 <i>H</i> -indole-4,7-dione 94	196
Figure 98: ^1H Spectrum of <i>tert</i> -butyl benzyl-4-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)but-3-ynylcarbamate 89	197
Figure 99: ^{13}C Spectrum of <i>tert</i> -butyl benzyl-4-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)but-3-ynylcarbamate 89	198
Figure 100: ^1H Spectrum of <i>tert</i> -butyl benzyl-2-(4,5-diisopropoxy-3,6-dioxocyclohexa-1,4-dienyl)ethylcarbamate 92	199
Figure 101: ^{13}C Spectrum of <i>tert</i> -butyl benzyl-2-(4,5-diisopropoxy-3,6-dioxocyclohexa-1,4-dienyl)ethylcarbamate 92	200
Figure 102: ^1H Spectrum of 4-hydroxy-2,3-diisopropoxy-4-(2-(2-nitrophenyl)ethynyl)cyclobut-2-enone 51a	201
Figure 103: ^{13}C Spectrum of 4-hydroxy-2,3-diisopropoxy-4-(2-(2-nitrophenyl)ethynyl)cyclobut-2-enone 51a	202

Figure 104: ^1H Spectrum of 2-(2-nitrobenzylidene)-4,5-diisopropoxycyclopent-4-ene-1,3-dione 51d	203
Figure 105: ^{13}C Spectrum of 2-(2-nitrobenzylidene)-4,5-diisopropoxycyclopent-4-ene-1,3-dione 51d	204
Figure 106: ^1H Spectrum of 2,3-diisopropoxy-5-(2-nitrophenyl)cyclohexa-2,5-diene-1,4-dione 51c	205
Figure 107: Expanded view of gHMBC Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[<i>b</i>]quinolin-1-ol 35a	206
Figure 108: Expanded view of gHMQC Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[<i>b</i>]quinolin-1-ol 35a	207

List of Schemes

Scheme 1: Skraup Quinoline Synthesis	2
Scheme 2: Doebner-von Miller Quinoline Synthesis	3
Scheme 3: Knorr Quinoline Synthesis	4
Scheme 4: Conrad-Limpach Quinoline Synthesis	4
Scheme 5: Similarities of the Conrad-Limpach and Knorr Quinoline Synthesis ...	5
Scheme 6: Friedländer Quinoline Synthesis	6
Scheme 7: Pfitzinger Quinoline Synthesis	7
Scheme 8: Ruthenium Catalyzed Quinoline Synthesis	8
Scheme 9: Microwave Assisted Quinoline Synthesis	8
Scheme 10: Natural Products Synthesized from Squarate Derivatives	10
Scheme 11: Synthesis of Assoanine from Dimethyl Squarate	11
Scheme 12: Initially Planned Reaction Sequence	13
Scheme 13: General Reaction Sequence for the Synthesis of Novel Quinolines	13
Scheme 14: Proposed Mechanism for the Formation of the Alkylidene	15
Scheme 15: Synthesis of the N-BOC Protected Starting Materials	19
Scheme 16: Alkylation of Diisopropyl Squarate	20
Scheme 16a: Alkylation of Diisopropyl Squarate with other N-BOC Protected Derivatives	22
Scheme 17: Alternate Method for the Synthesis of Alkylation Products	23
Scheme 18: Expansion, Deprotection and Reduction of BOC Protected Derivatives	25
Scheme 19: Air Oxidation of the Quinolinol	26
Scheme 20: Reaction Sequence for the Semisquarate Derivative	27
Scheme 21: Alkylation Diisopropyl Squarate with 45	28
Scheme 22: Alkylation Diisopropyl Squarate with 47	28
Scheme 23: Sonogashira Coupling of the Acetanilide (49) and <i>N</i> -benzyl (50) Derivatives	30
Scheme 24: Thermal Ring Expansion of the Acetanilide	30
Scheme 25: Sonogashira Coupling of 2-Iodonitrobenzene	32
Scheme 26: Thermal Ring Expansion of Nitrobenzene Derivative	32
Scheme 27: Thermal Ring Expansion of a Cyclobutenone Substituted Indole ..	35
Scheme 28: Base Mediated Indolization	36
Scheme 29: Copper Mediated Indolization	36
Scheme 30: Copper Acetate Catalyzed Indolization	37
Scheme 31: Palladium Catalyzed Indolization	38
Scheme 32: <i>N</i> -Iodosuccinimide Mediated Ring Expansion	39
Scheme 33: <i>N</i> -Chlorosuccinimide Mediated Ring Expansion	39
Scheme 34: Palladium Catalyzed Ring Expansion	40
Scheme 35: Base Mediated Indolization	41
Scheme 36: Copper Mediated Reaction Scheme for <i>N</i> -BOC Protected 28a	42
Scheme 37: Copper Iodide Mediated Indolization for <i>N</i> -Benzyl Protected 48 ...	44
Scheme 38: Copper Acetate Catalyzed Indolization	45
Scheme 39: Attempted <i>N</i> -Iodosuccinimide Mediated Ring Expansion	46

Scheme 40: Attempted <i>N</i> -Chlorosuccinimide Mediated Ring Expansion	47
Scheme 41: Halide Mediated Cyclobutenone Rearrangement.....	47
Scheme 42: Existing Synthesis of <i>Drupella fragum</i> Indoloquinones 79 and 82	51
Scheme 43: Alkylation of 27 with 83 and 87	52
Scheme 44: Ring Expansion and Cyclization of 89 to 91	53
Scheme 45: Proposed Mechanism for the Tandem Expansion/Cyclization of 89	54
Scheme 46: Debenzylation of 91	55
Scheme 47: DDQ Oxidation of 91 to 94	55
Scheme 48: Proposed Route for the Synthesis of 79	56
Scheme 49: Ring Expansion of 89 to Quinone 92	56
Scheme 50: Acidic Deprotection of 92 to 91	57
Scheme 51: Proposed Future Research with Butyne Derivatives	57

List of Tables

Table 1: Summary of NMR Data for the Structural Determination of 35a	14
Table 2: Alkylation Conditions of 26a to give 28a	20
Table 3: Alkylation Conditions for 47	29
Table 4: Copper Mediated Reaction Conditions for 28a	43
Table 5: Copper Mediated Reaction Conditions for 28a	94

Part I

A Novel Entry to Cyclopenta[*b*]quinolines *via* Thermal Ring-Expansion of (2-Aminophenyl)-Ethynyl-Substituted Cyclobutenone Derivatives

1. Introduction

Quinoline derivatives are found in a significant number of natural products and pharmaceuticals.¹ These alkaloids exhibit a wide array of biological activities including antimalarial, antibacterial, antidiabetic, anti-inflammatory² and antitumor behaviors.³ Examples of biologically active quinolines are quinine and 20-(S)-camphothecin. Quinine (**1**)⁴ and 20-(S)-camphothecin (**2**)³ exhibit antimalarial and excellent antitumor activities, respectively (Figure 1).

Figure 1: Biologically Active Quinolines

Due to the significant biological activity exhibited by quinolines, development of novel synthetic methods of the quinoline core is of great interest to researchers.

Classical syntheses of quinolines typically fall into one of two major classes, cyclization of monosubstituted benzenes, usually *N*-substituted anilines, and cyclizations of ortho-disubstituted benzenes. The first class includes the Skraup, Doebner-von Miller, Knorr and Conrad-Limpach reactions as well as numerous modifications thereof and several less utilized reactions.⁵ The second major class of quinoline syntheses involves either an intramolecular or intermolecular condensation of ortho-disubstituted benzenes. These synthetic methods include the Friedländer and Pfitzinger reactions in addition to several minor variations.⁵

1.1. Quinoline Syntheses: Intramolecular Cyclization of Anilines

The Skraup⁶ reaction is one of the oldest methods for the synthesis of quinolines.⁵ For example, quinoline (**5**) was obtained in moderate yield by heating aniline (**3**), glycerol (**4**) and sulfuric acid in nitrobenzene (Scheme 1). This reaction sequence occasionally suffers from the disadvantage of proceeding with extreme violence.^{5,7} Moderators such as acetic or boric acid were eventually added to avoid the fierce nature of these reactions. The reaction is thought to proceed through a Schiff base from the condensation of acrolein, generated *in situ*, with aniline followed by acid mediated cyclization. Acrolein is known to be the product of acidic treatment of glycerol.⁷

Scheme 1: Skraup Quinoline Synthesis

Doebner and von Miller⁸ modified the Skraup procedure by substituting ethylene glycol (**6**) for glycerol. 2-Methylquinoline (**7**) was prepared in good yield by the apparent Michael addition of the aniline to crotonaldehyde formed *in situ* from ethylene glycol (Scheme 2).⁷ Crotonaldehyde is formed via aldol condensation of acetaldehyde in turn formed from ethylene glycol. Mechanistically, the Doebner von-Miller is similar to the Skraup reaction.

Scheme 2: Doebner-von Miller Quinoline Synthesis

The Knorr⁹ quinoline synthesis was the first cyclization involving an acetanilide intermediate. Knorr was able to demonstrate his reaction sequences were applicable to acetoacetylated aryl amines with vacant ortho positions. For example, 2-hydroxy-4-methylquinoline (**9**) was formed in good yield from the reaction of ethyl acetoacetate (**8**) with aniline (Scheme 3). Formation of the acetanilide intermediate is fairly straightforward. The aniline nitrogen attacks the ester carbonyl of the β -ketoester, which loses an equivalent of alcohol and forms the acetanilide. Cyclization and dehydration is brought about by the heating of the acetanilide in the presence of acid, forming a quinolone intermediate. The quinolone then tautomerizes to produce a hydroxyquinoline.¹⁰

Scheme 3: Knorr Quinoline Synthesis

Conrad and Limpach¹¹ developed a milder approach to quinoline formation with regiochemical outcomes different from the Knorr reaction. 4-Hydroxy-2-methylquinoline (**10**) was obtained in moderate yield from the acid catalyzed reaction of aniline and ethyl acetoacetate (Scheme 4).¹² The aniline nitrogen condenses with the β -carbonyl carbon of the β -ketoester to form an enamine intermediate. Two mechanisms have been suggested for the formation of the quinoline upon heating. The first mechanism involves enolization of the enamine, 6π electrocyclization, loss of alcohol and tautomerization. The second mechanism suggested involves the loss of alcohol to give a ketene, 6π electrocyclization and tautomerization.¹⁰

Scheme 4: Conrad-Limpach Quinoline Synthesis

The regiochemical outcome of the Conrad-Limpach reaction can be affected by the careful adjustment of the reaction conditions. The anilide (**11**) and enamine

(**12**) could be interconverted in the presence of an acid catalyst and an appropriate drying agent at room temperature or by gentle heating. However, the Conrad-Limpach enamino-ester intermediate (**12**) cannot be converted to the Knorr regiochemistry with direct acidic treatment (Scheme 5).¹⁰ Heating **12** produces 4-Hydroxy-2-methylquinoline (**10**). Acid mediated cyclization and dehydration of **11** produces **9a**, which tautomerizes to **9**.

Scheme 5: Similarities of the Conrad-Limpach and Knorr Quinoline Synthesis

Synthesis

1.2. Quinoline Syntheses: Cyclization of Ortho-Disubstituted Benzenes

The Friedländer¹³ synthesis typically involves the condensation of an *ortho*-amino aldehyde or ketone with another aldehyde or ketone to produce the quinoline core. This reaction sequence is somewhat limited in scope since the *ortho*-amino benzaldehydes are susceptible to self condensation. An intermediate (**15**) in a synthesis of mappicine was prepared in excellent yield using a protected 2-aminobenzaldehyde **13** and ketone **14** (Scheme 6). Two mechanisms have been

proposed for the Friedländer reaction. The first proposed mechanism proceeds through the formation of the imine followed by an intramolecular Claisen condensation. The second mechanism proposed an intermolecular Claisen condensation followed by cyclization *via* imine formation.¹⁰

Scheme 6: Friedländer Quinoline Synthesis

Pfizinger¹⁴ improved the Friedländer synthesis by the use of isatin (**16**) which is significantly more stable than the Friedländer starting materials.¹⁰

2-Methylquinoline-4-carboxylic acid (**18**) was synthesized in excellent yield through a Friedländer type reaction (Scheme 7).¹⁵ The mechanism probably proceeds *via* isatic acid (**17**), is formed from base mediated ring opening of isatin (**16**), followed by an intermolecular condensation to form a Schiff base, usually with acetone. Cyclization of the Schiff base *via* Claisen condensation occurs between the benzylic carbonyl and the α -methylene of the imine intermediate.¹⁰

Scheme 7: Pfitzinger Quinoline Synthesis

1.3. Modern Quinoline Syntheses

More modern syntheses have been developed which are significantly milder than the “witch’s brews” of many of the classical methods. A catalytic ruthenium-grafted hydrotalcite (HT) route has been developed. This method uses an amino benzyl alcohol (**19**), an acetophenone (**20**) in the presence of molecular oxygen. 2-Substituted quinolines are formed from this reaction. As an example, compound **21** was formed in good yield. This reaction is superior to the Friedländer reaction since the starting materials are more stable. This is also the first reported example one-pot quinoline synthesis using heterogeneous catalysts. The catalyst was formed by mixing a dilute solution of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ with hydrotalcite ($\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3$) and triethylamine. During the development of this catalyst system it was noticed that no reaction occurred in the absence of an amine (designated as N) or the ruthenium (Scheme 8).¹⁶

Scheme 8: Ruthenium Catalyzed Quinoline Synthesis

Microwave-assisted reaction technology of small organic molecules has become an attractive tool in organic synthesis. Microwave reactors are simple to operate and significantly enhance reaction rates. A three-component one-pot quinoline synthesis has been developed using aryl aldehydes, aryl amines and alkynes. Brief pulsed microwave irradiation of **22**, **23** and **24** in the presence of a copper (I) salt impregnated montmorillonite clay gave the complex quinoline (**25**) in excellent yield (92%) (Scheme 9).² In the absence of the montmorillonite clay the reactions typically produced poor yields.

Scheme 9: Microwave Assisted Quinoline Synthesis

1.4. Cyclobutenediones

Cyclobutenediones, “squarate” derivatives, have been shown to be highly versatile C₄-synthons that can undergo thermal rearrangement. These building

blocks and have been utilized for the synthesis of many polysubstituted cyclic compounds including heterocycles.¹⁷ Thermally induced ring-expansions of 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones are known to produce both 1,4-benzoquinones and 5-alkylidenecyclopentenediones.¹⁸ In general, alkyl-substituted alkynes offer clean conversion to quinones,¹⁹ whereas TMS-alkyne, alkynes with electron-withdrawing groups or alkenyl-substituted alkynes affords only 5-membered products. Alkynes with electron-donating groups, and aryl-substituted alkynes afford mixtures of 5- and 6-membered rings. Several natural products such as assoanine,^{19f} perezzone, isoperezzone,²⁰ echinochrome A²¹ and pentalenene²² have been synthesized from squaric acid derivatives (Scheme 10). An example of the squarates being used in an alkylation ring expansion fashion is the synthesis of assoanine. Dimethyl squarate **25b** was alkylated with propargyl alkyne **25a** to give **25c** in 87% yield. Thermal ring expansion and cyclization in *p*-xylene at 138 °C yielded the tetracyclic hydroxyquinone intermediate **25d** in 40% yield. Subsequent conversion to the diphosphonate ester followed by reduction gave assoanine in 18% yield over two steps (Scheme 11). Due to the versatility of the squarates we sought to use them to synthesize novel heterocycles.

Scheme 10: Natural Products Synthesized from Squarate Derivatives

Scheme 11: Synthesis of Assoanine from Dimethyl Squarate

2. Results and Discussion

Thermal reactions of alkyne substituted cyclobutenone derivatives were examined as a part of a larger project to prepare complex heterocyclic compounds. We envisioned a synthesis proceeding *via* a ring-expansion of 4-hydroxy-2-cyclobuten-1-ones having heteroatoms tethered to the cyclobutenone in the 4-position *via* an alkyne (Scheme 12).

2.1. N-BOC Protected Derivatives

In our initial reaction, compound **28a** was obtained *via* dilithiation of the *N*-protected 2-aminophenylalkyne **26a** followed by alkylation with 2,3-bis(1-methylethoxy)-2-cyclobuten-1,4-dione (diisopropyl squarate **27**). Cyclobutenone **28a** was dissolved in toluene and heated at reflux overnight. Workup and purification by chromatography on silica gel gave a new compound initially thought to be the 1,4-quinone **29** based on NMR data. Deprotection of the putative compound produced a new product seemingly derived from the formation of a quinone-imine **31**. However, upon attempted sodium borohydride reduction of **31**, the spectral data of the product did not correspond to the expected hydroxycarbazole **32**. A new methine having a carbon resonance at 68.9 ppm and its corresponding proton resonance at 5.05 ppm was observed. These resonances cannot be assigned to any of the carbons or protons expected for hydroxycarbazole **32**. Submitting the reduction product to gHMQC (gradient Heteronuclear Multiple Quantum Coherence, one bond ^1H and ^{13}C hetero-correlation) (Figure 2) and gHMBC (gradient Heteronuclear Multiple Bond Coherence, two to four bond ^1H and ^{13}C hetero-correlation) (Figure 3) NMR experiments revealed that the product was in fact the fused quinolinol **35a** and not the hydroxycarbazole **32**. The ^1H , ^{13}C , gHMBC and gHMBC data are summarized in Table 1. This in turn means that the ring-expansion did not yield the 1,4-quinone **29** but its five-membered counterpart **33a**. It should be noted that, this reaction was very selective with regard to ring-size. Only the five-membered ring was observed by ^1H NMR of the crude reaction mixture and the

purified product. Subsequent removal of the BOC group gave the fused quinoline **34a** and reduction yielded the fused quinolinol **35a** (Scheme 13).

Scheme 12: Initially Planned Reaction Sequence

Scheme 13: General Reaction Sequence for the Synthesis of Novel Quinolines

Table 1: Summary of NMR Data for the Structural Determination of 35a

Position	δ_C	δ_H^a	HMBC
1	68.9	5.05 s	C-2, C-3, C-9a, C-3a, C-9
2	159.8		
3	151.2		
3a	131.1		
4			
4a	126.4		
5	128.0	7.64 d	C-8a, C-7, C-4a, C-8
6	124.9	7.36 t	C-8, C-4a, C-7
7	128.8	7.56 t	C-8a, C-5, C-9, C-8
8	128.6	7.97d	C-4a, C-6
8a	148.4		
9	128.2	7.78 s	C-2, C-8a, C-9a, C-1, C-8, C-6, C-4a
9a	133.9		

Note: a) Correlations of ^1H and ^{13}C made by gHMQC (Figure 2)

The proposed mechanism of the ring expansion of **28a** is depicted in Scheme 14. The mechanism probably proceeds through the electrocyclic ring opening of **28a** to give ketene **29a** followed by the 5-endo-dig cyclization forming intermediate **29d**. Subsequent hydrogen atom abstraction followed to give the diradical **29e** and later 5-alkylidenecyclopentendione (**33a**). The anticipated mechanism for the ring expansion to give the 1,4-benzoquinones also depicted in Scheme 14. It should be noted that this mechanistic pathway did not occur since we did not observe the benzoquinone. The mechanism would probably proceed through the electrocyclic ring opening of **28a** to give ketene **29a** followed by the 6-endo-dig cyclization forming intermediate **29b**. Subsequent hydrogen atom abstraction followed to give the diradical **29c** and later 1,4-quinone formation (**29**).

Scheme 14: Proposed Mechanism for the Formation of the Alkylidene

Figure 2: Gradient Heteronuclear Multiple Quantum Coherence Spectrum of

With this novel route to highly functionalized fused quinolines in hand the scope and limitations were examined. The starting materials were prepared from 2-iodoarylamines *via* a sequence of steps consisting of *N*-BOC protection of the amino group, Sonogashira coupling using ethynyl trimethylsilane and desilylation. The first three steps generally proceeded smoothly and often in excellent yield (Scheme 15). The *N*-BOC protection reactions proved best when the free aniline was treated with excess NaHMDS²³ followed by the dropwise addition of a BOC₂O/THF solution. Several other reaction conditions were attempted for the *N*-BOC protection of the anilines, but all gave poor yields of products. The Sonogashira²⁴ reactions initially gave a significant amount of homocoupling of trimethylsilyl acetylene product which were hard to separate from the desired product. The homocoupling problem was alleviated by reducing the amount of the alkyne from 1.1 equivalents to 1.05 equivalents. The two methods^{65,25} used for the desilylation of the TMS-protected products (**38b-38e**), NaOH and KF. Deprotection using NaOH often gave higher yields however, the KF method was significantly faster. In addition, the KF method was superior to the NaOH method for the pyridine derivative (**38e**).

Scheme 15: Synthesis of the N-BOC Protected Starting Materials

Notes: a) NaOH, EtOH b) KF, MeOH

The terminal alkynes were dilithiated and reacted with diisopropyl squarate. The alkylations were problematic and significant amounts of the alkyne starting material was often recovered (Scheme 16). One explanation for recovering significant amounts of the starting alkyne could be due to lower solubility of the dianion in the colder solutions. Multiple reaction conditions were investigated to optimize the alkylation conditions (Table 2).

Scheme 16: Alkylation of Diisopropyl Squarate

Table 2: Alkylation Conditions of 26a to give 28a

Entry	Base	Reaction Conditions	Yield 28a
1 ^a	2.0 eq. <i>n</i> -BuLi	-78 °C, 20 min., then 27 , -78 °C, 30 min.	48%
2 ^a	2.5 eq. <i>n</i> -BuLi	-78 °C, 20 min., then 27 , -78 °C – rt, 30 min.	62% ^c
3 ^b	3.0 eq. <i>n</i> -BuLi	-78 °C, 20 min., then 27 , -78 °C, 30 min.	NR
4 ^b	2.5 eq. <i>t</i> -BuLi	-78 °C, 30 min., then 27 , -78 °C – rt, 1h.	unidentifiable
5 ^b	2.5 eq. <i>t</i> -BuLi	-78 °C, 30 min., then 27 , -78 °C – rt, 30 min.	31%
6 ^b	3.0 eq. <i>t</i> -BuLi	-78 °C, 1h., then 27 , -78 °C – rt, 12h	unidentifiable
7 ^b	2.5 eq. <i>n</i> -BuLi	-78 °C 1h, to -20 °C, 1h., then 27 , -78 °C – rt, 1h.	unidentifiable
8 ^a	2.5 eq. <i>t</i> -BuLi	-78 °C, 30 min., then 27 , -78 °C – rt, 1h.	20%
9 ^a	2.5 eq. NaHMDS	-78 °C, 1h, then 27 , -78 °C, 18h.	NR
10 ^a	2.5 eq. <i>n</i> -BuLi	-78 °C, 1h, then 27 , CeCl ₃ , -78 °C, 1h.	NR
11 ^b	2.5 eq. <i>n</i> -BuLi	-10 °C, 15 min., then 27 , -10 °C, 30 min.	64% ^d

Notes: All reactions in this table used 1 equivalent of **26a** and **27** a) The dilithiated aniline was added to the squaric acid derivative, b) The squaric acid derivative was added to the dilithiated aniline c) High yield obtained in one case, repeated reaction gave inconsistent results d) Consistent results

It should also be noted that adding two equivalents of the alkyne (**26a**) gave only a 64%, based on the converted squarate, yield of **28a**. This reaction sequence was subsequently abandoned since only approximately 30% of the alkyne **26a** was converted. It was discovered that the conditions of entry 11 gave the most consistent alkylation results. Therefore, these conditions were used without modification for the alkylation of the other derivatives (**26b-26d**) with the exception of the pyridine (**26e**). It was found that the pyridine derivative (**28e**) was obtained in slightly higher yields (approximately 10%) when allowed to warm to room temperature over the last 10 minutes of the reaction, prior to quenching. Upon alkylation of the 5-methoxy-substituted substrate (**26c**), an inseparable mixture of the expected alkylation product **28c** and alkylation of the squarate **27** with excess butyl lithium was isolated (structure not shown) (Scheme 16). Alkylation of diisopropyl squarate (**27**) was only seen in the case of the 5-methoxy-substituted substrate (**26c**) (Scheme 16a).

Scheme 16a: Alkylation of Diisopropyl Squarate with other N-BOC

Protected Derivatives

Notes: a) Inseparable mixture with the butyl addition product of diisopropyl squarate, b) The reaction was warmed to room temp for 10 minutes prior to quench

The Sonogashira reaction was also briefly investigated as an alternative to deprotonation and alkylation of the *N*-protected ethynyl anilines. Squarate derivative²⁷ **39** was stirred briefly with 5% Pd(PPh₃)₂Cl₂ and 5% CuI in triethylamine followed by the addition of *N*-protected aryl iodide **37a** were allowed to stir overnight at room temperature. Unfortunately, a low yield of the anticipated product **28a** was obtained. Addition of a full equivalent of CuI was found to increase the yields. Generally, the deprotonation route was better except in one case (Scheme 17). Apart from the anisole derivative **28c** that was cleanly synthesized in 65% yield, the deprotonation-alkylation route gave a better yield of product. We were somewhat surprised that the toluene derivative (**37d**) did not react under the Sonogashira reaction conditions.

Scheme 17: Alternate Method for the Synthesis of Alkylation Products

Notes: a) 5% CuI added, b) 1 equivalent of CuI was added, c) based on recovered iodide

With a number of alkyne-cyclobutenones in hand the ring expansion to form cyclopenta[*b*]quinolines was examined (Scheme 18). Thermal ring-expansion of **28a-28e** gave in all cases the expected cyclopentenediones **33a-33e**. Toluene was found in general to be a good solvent for the ring expansions with the exception of the pyridine derivative. However, a cleaner conversion of the pyridine **33e** was observed in 1,2-dichloroethane (1,2-DCE).⁷⁰ Again, all thermal reactions were selective with regard to ring-size, and only five-membered rings were observed by ¹H NMR. Acidic removal of the BOC-group and spontaneous cyclization gave the expected cyclopenta[*b*]quinoline-1-ones **34a-34e**. The pyridine derivative (**33e**) proved to be more difficult to deprotect compared to the toluene (**33d**), anisole (**33c**) and chloro (**33b**) derivatives. HCl in EtOAc or HCl in MeOH for the *N*-deprotection of the pyridine derived compound yielded neither starting material nor any product. The use of TMSI²⁸ is typically a very fast method for the removal of *N*-BOC groups, however, in the case of **33e** only 3% of the fused aza-quinolone **34e** was obtained. Trifluoroacetic acid in CH₂Cl₂ at

reflux was the only successful deprotection of the pyridine and yielded the aza-quinolone **34e** in 86% yield. Finally, sodium borohydride reduction of **34a-34e** furnished the cyclopenta[*b*]quinoline-1-ols **35a-35e** (Scheme 17). The reduction product **35e** was not fully characterized due to rapid decomposition and was therefore only tentatively assigned as the aza-quinolinol.

¹H NMR data was used to identify which stage the reactions were. We were able to identify the basic structures by observing the chemical shifts of the isopropyl methine (heptets) and the isopropyl methyls (doublets). Upon reduction we were also able to track the new methine formed. The typical range for the resonances of the alkylation products (**28a-28e**) ranged from 4.90-4.85 and 5.02 for the methine signals and 1.47-1.46 and 1.32-1.29 for the isopropyl methyls. For the ring expansion (**33a-33e**) the methine protons ranged from 5.61-5.55 as overlapping heptets, the methyl doublets overlapped with a range of 1.42-1.36. The quinolinone (**43a-43e**) methines ranged from 5.72-5.62 and 5.32-5.23 as separate signals, the methyl resonances ranged from 1.48-1.51 and 1.34-1.38 as separate signals. The quinolinol (**35a-35d**) methine signals ranged from 5.25-5.38 and 5.12-5.15 as separate signals and the methyls 1.37-1.34. The new methine for the reduction ranged from 5.01-5.06 ppm.

Scheme 18: Expansion, Deprotection and Reduction of BOC Protected Derivatives

28a R=H, X=CH
28b R=4-Cl; X=CH
28c R=5-OMe, X=C
28d R=5-Me, X=C
28e R=H, X=N

33a 82%^a
33b 78%^a
33c 39%^{a,b}
33d 83%^a
33e 78%^c

34a R=H, X=CH 66%^d, 74%^e
34b R=4-Cl; X=CH 54%^d
34c R=5-OMe, X=C 78%^d
34d R=5-Me, X=C 70%^d
34e R=H, X=N 3%^f, 86%^e

35a 84%
35b 68%
35c 70%
35d 70%
35e 51%^g

Notes: a) In refluxing toluene, b) Yield calculated over two steps, c) refluxing 1,2-DCE, d) HCl was used for the deprotection e) TFA was used for the deprotection f) TMSI was used for the deprotection g) Tentative assignment due to rapid decomposition

The cyclopenta[*b*]quinoline-1-ols (**35a-35d**) were slowly oxidized to the corresponding cyclopenta[*b*]quinoline-1-ones (**34a-34d**) upon standing in air as determined *via* ¹H NMR, the yields were not calculated for this oxidation (Scheme 19).

Scheme 19: Air Oxidation of the Quinololinol

As a final example, 3-(1-methylethoxy)-4-methyl-3-cyclobutene-1,2-dione⁶⁹ was reacted with the dianion formed from **26a** to give the expected alkylation product **41** as a single regioisomer in 48% (59% based on recovered **26a**). The alkylation occurred on the more electrophilic carbonyl carbon. The carbonyl in conjugation with the alkoxy-group is typically less reactive due to resonance contributions from the alkoxy oxygen. Ring-expansion of **41** in 1,2-DCE at reflux furnished the expected cyclopentendione **42** as an 8.3:1 E/Z (by NMR integration) mixture in 49% overall yield. A poor yield of **42** was obtained in refluxing toluene. The E-isomer has previously been shown to be the kinetic product from ring-expansions of related compounds.²⁹ Although condensation of the free amine with the carbonyl having a conjugated alkoxy-group is expected to be much slower, we were surprised to observe only one isomer (**43**) upon BOC-protecting group removal. The product is derived from cyclization of the thermodynamically more stable Z-isomer. This observation can be explained by a facile E to Z isomerization of the alkene prior to cyclization. Isomerization of **E-42** to **Z-42** was observed by ¹H NMR simply by allowing the NMR sample to sit for a few hours at ambient temperature. Reduction of **43** gave **44** however, this compound was not fully characterized due to very rapid decomposition and was

only tentatively assigned as **44** (Scheme 20). ^1H and ^{13}C NMR spectra of **44** were in full agreement with the structure of **44**.

Scheme 20: Reaction Sequence for the Semisquarate Derivative

2.2. *N*-Acetyl and *N*-benzyl aniline

As a subproject to the *N*-BOC protected anilines two additional amino protective groups were studied. Our goal was to test the theory that a change in the amino protecting group would affect the thermal ring expansion *i.e.* 5- versus 6-membered ring formation. The *N*-acetyl and the *N*-benzyl protective groups were studied. The *N*-acetyl³⁰ (**45**) and *N*-benzyl³¹ (**47**) derivatives were synthesized according to literature procedures. Diisopropyl squarate (**27**) was alkylated by

the *N*-acetyl derivative (**45**) in 72% yield by the addition of the dianion to the squarate derivative. The yields were approximately 20% lower when the squarate was added to the dianion (Scheme 21). Alkylations using *N*-Benzyl aniline (**47**) proved to be very problematic and only poor yields were obtained (Scheme 22). Multiple conditions for the alkylation of the *N*-benzyl derivative (**47**) were investigated all giving disappointing results (Table 2). It should also be noted that alkylation of the free aniline (not depicted) gave unidentifiable products.

Scheme 21: Alkylation of Diisopropyl Squarate with 45

Scheme 22: Alkylation of Diisopropyl Squarate with 47

Note: a) Yield based on recovered **47**

Table 3: Alkylation Conditions for 47

Trial	Base	Reaction Conditions	Yield of 48
1	1.05 eq. <i>n</i> -BuLi	-40 °C, 15 min., then 27 , -40 °C, 30 min.	19%, 50% ^a
2	1.05 eq. <i>n</i> -BuLi	-10 °C, 15 min., then 27 , -10 °C, 30 min.	24%, 39% ^a
3	2.05 eq. <i>n</i> -BuLi	-10 °C, 30 min., then 27 , -10 °C - rt, 1h.	14%
4	1.7 eq. <i>n</i> -BuLi	-10 °C, 15 min., then 27 , -10 °C - rt, 30 min.	NR
5	1.7 eq. <i>n</i> -BuLi	-10 °C, 20 min., then 27 , -10 °C - rt, 30 min.	10%
6	1.7 eq. <i>n</i> -BuLi	-10 °C, 20 min., then 27 , -10 °C - rt, 1h.	21%, 26% ^a
7	1.1 eq. <i>n</i> -BuLi	-10 °C, 15 min., then 27 , -10 °C - rt, 30 min.	23%
8	1.5 eq. <i>n</i> -BuLi	-10 °C, 15 min., then 27 , -10 °C - rt, 30 min.	7%, 9% ^a
9	1.1 eq. NaHMDS	-10 °C, 10 min., then 27 , -10 °C, 30 min.	10%, 12% ^a
10	1.1 eq. NaHMDS	-40 °C, 30 min., then 27 , -40 °C, 1h.	9%, 12% ^a
11	1.1 eq. <i>n</i> -BuLi	Et ₂ O, -78 – 0 °C, 30 min., then 27 , Et ₂ O, 0 °C 30 min.	10%

NOTE: Yield based on recovered **47**

The Sonogashira reaction was also briefly investigated for the *N*-acetyl and *N*-benzyl derivatives. Squarate derivative²⁷ (**39**) was briefly slurried with 5% Pd(PPh₃)₂Cl₂, and one equivalent of CuI in triethylamine and then the protected aryl iodides were added and the resulting reaction mixture was allowed to stir overnight at ambient temperature. The coupling of the *N*-acetyl (**49**) and *N*-benzyl (**50**) derivatives gave the desired products in 45% and 4%, respectively. In both cases the deprotonation-alkylation procedure, especially in the *N*-acetyl case, was found to be a superior method (Scheme 23).

Scheme 23: Sonogashira Coupling of the Acetanilide (49**) and *N*-benzyl (**50**) Derivatives**

Note: a) Based on recovered **49**

The alkylated *N*-acetyl protected compound **46** gave a good yield (72%) of alkylidene **51** upon thermal ring expansion in toluene at reflux (Scheme 24). The *N*-benzyl alkylation product **48** on attempted thermal ring expansion yielded only unidentifiable products in toluene at reflux and did no reaction was observed in 1,2-DCE at reflux with no starting material being recovered. The *N*-benzyl derivative was not further examined.

Scheme 24: Thermal Ring Expansion of the Acetanilide

Although the yield of the ring-expanded N-acetyl protected product **51** was good we were unable remove amino protecting group using dilute HCl at reflux or hydrazine at reflux.

2.3. Nitrobenzene Derivative

The functional group was changed from a *N*-protected aniline to a nitro group. This subproject examined the effect of the electron withdrawing group on the thermal ring expansion. Alkylation of **27** with ethynyl nitrobenzene did not give the expected product, instead the Sonogashira reaction was investigated for nitro derivative **51a**. Squarate derivative²⁷ **39** was stirred briefly with 5% Pd(PPh₃)₂Cl₂ and 5% CuI in triethylamine followed by the addition of 2-iodonitrobenzene **51b**. Unfortunately, a 9% yield of the anticipated product **51a** was obtained. Addition of a full equivalent of CuI was found to increase the yields to 53% **51a** (Scheme 25). Thermal ring expansion gave two products, the quinone **51c** in 11% yield and the alkylidene **51d** in 33% yield (Scheme 26). The assignments were made based the quinone and alkylidene protons, as compared to literature values of ring-expanded squarates.²⁹ The literature values reported for a squarate based alkylidene and quinone were a singlet at 7.41 ppm a singlet at 6.70 ppm, respectively. Compound **51d** has a singlet at 7.69 ppm and **51c** showed up at 6.47 ppm. The electron withdrawing group seems to have a greater selectivity for the 5-membered ring versus the 6-membered ring formation. We were pleased to discover the 6-membered ring can be obtained from aryl-alkyne ring

expansion, however we were disappointed in the subsequent yield of the quinone.

Scheme 25: Sonogashira Coupling of 2-Iodonitrobenzene

Scheme 26: Thermal Ring Expansion of Nitrobenzene Derivative

3. Conclusions

A novel route to cyclopenta[*b*]quinoline-1-ones and -ols has been developed. Substituted cyclopenta[*b*]quinolin-1-ones were prepared by thermal ring-expansion of substituted *N*-BOC protected 4-(2-aminophenylethynyl)-4-hydroxy-2-cyclobuten-1-ones forming the corresponding 2-aminophenylmethylidene substituted 4-cyclopentene-1,3-diones. Deprotection of the amine resulted in spontaneous condensation to give cyclopenta[*b*]quinolin-1-ones. Sodium

borohydride reduction of these products produced cyclopenta[b]quinolin-1-ols. The key step in the sequence is a thermally induced ring-expansion of 4-(2-aminophenylethynyl)-4-hydroxy-2-cyclobuten-1-ones. Changing the amino protecting group had no effect on the ring size selectivity of the thermal ring expansion. The thermal ring expansion of the nitro derivative suggests that electron withdrawing substituents may slightly alter the size selectivity of the ring formation.

Part II

Attempted Indolizations and Additional Ring Expansions

1. Introduction

Heterocycles play a central role in organic and medicinal chemistry since many of these compounds exhibit useful properties.³² The indole nucleus is found in a significant number of biologically active, naturally occurring products³³ and are extremely valuable in medicinal chemistry.³⁴ Common methods for indolization of 2-ethynylanilines include base,³⁵ and transition metal mediated and catalyzed cyclizations.³⁶

Ring-expansions of 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones to give 5-alkylidenecyclopentenediones have been reported that use palladium complexes and electrophilic reagents such as N-iodosuccinimide³⁷, NIS, and N-chlorosuccinimide, NCS.³⁸ We envisioned using these different indolization methods to form the indole nucleus followed by a ring expansion/cyclization sequence to afford carbazolequinones. We also wanted to use the ring expansion routes to tune the product ring size of the squarate portion of the molecules to afford either a 1,4-quinone or a alkylidene cyclopentendione. The synthesis of carbazolequinones using cyclobutenone substituted indoles has been reported (Scheme 27).³⁹ Squarate **67a** was alkylated with **67b**. The reaction was quenched with acetic anhydride and worked up giving **67c**.

Compound **67c** was then immediately thermalized and oxidized with ceric ammonium nitrate, CAN, to give **67d** as a single regioisomer.

Scheme 27: Thermal Ring Expansion of a Cyclobutenone Substituted Indole

1.1. Indolization Methods

Base mediated cyclization methods have been used extensively to form the indole nucleus.⁴⁰ Silyl alkyne **52** was cyclized to give **53** (70% yield) in the presence of potassium *tert*-butoxide in *tert*-butanol at 83°C (Scheme 28).⁴¹ The proposed mechanism involves the deprotonation of the carbamate nitrogen followed by attack on the alkyne forming a 2-trimethylsilyl 1-*tert*-butoxycarbonylindole intermediate. Subsequent hydrolysis cleaves the *tert*-butoxycarbonyl and trimethylsilyl groups.⁴⁰

Scheme 28: Base Mediated Indolization

In the early 1960s Castro *et al.* developed copper (I) mediated methods for the cyclization of aminoalkynes to produce indoles.⁴² The 2-substituted indole **55** was synthesized in the presence of CuI (2 equivalents) in DMF at 136 °C in 45% yield (Scheme 29). The mechanism probably involves the copper complexing with the alkyne followed by intramolecular attack by the amino group. The subsequent steps likely involve a proteolytic cleavage of an intermediate σ -alkenylcopper complex forming the indole nucleus.⁴³

Scheme 29: Copper Mediated Indolization

Copper acetate has also been used to catalyze the formation of the indole nucleus from various *N*-protected ethynylamines. The indole moiety in a synthesis of hippadine (**58**) was formed in 80% yield by copper (II) acetate

catalysis in 1,2-DCE at 83 °C (Scheme 30). The mechanism is thought to be similar to the CuI reactions.⁴⁴

Scheme 30: Copper Acetate Catalyzed Indolization

Palladium (II) complexes can also catalyze the amination and cyclization of alkynes to form the indole core.⁴⁵ An indole intermediate **60** in the synthesis of **61** was formed via palladium catalyzed amination of the alkyne (Scheme 31).⁴⁶ Compound **61** is known to suppress apoptosis in human cells. The mechanism probably involves the coordination of the palladium to the alkyne followed by an intramolecular attack by the amino group to form the metallo-indole intermediate. The subsequent steps probably involve a proteolytic cleavage of the intermediate σ -alkenylpalladium complex thus forming the indole nucleus.⁴⁵

Scheme 31: Palladium Catalyzed Indolization

1.2. Electrophilic Ring Expansions 4-Hydroxy-2-cyclobuten-1-ones

N-iodosuccinimide (NIS) mediated ring expansion has been used to form 5-alkylidenecyclopentenediones from 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones. The electrophilic ring expansion of **62** in the presence of excess NIS gave alkylidene **63** in 44% yield (Scheme 32). Two mechanisms have been suggested. The first step likely involves an I^+ transfer to the hydroxyl group to form a hypoiodite intermediate. This intermediate then probably induces a 1,2-acyl migration to the alkyne followed by the iodination forming the iodoalkylidene **63**. The other possible mechanism involves the formation of an iodonium ion with the alkyne followed by a 1,2-acyl migration forming **63**.⁴⁷

Scheme 32: *N*-Iodosuccinimide Mediated Ring Expansion

N-chlorosuccinimide (NCS) has recently been used in ring expansions of 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones.⁴⁸ Quinones **65a** and **65** were produced in 40% and 35%, respectively. The mechanism is likely to involve thermal ring-expansion followed by radical chlorination of the diradical intermediate (Scheme 33).

Scheme 33: *N*-Chlorosuccinimide Mediated Ring Expansion

Palladium catalyzed ring expansion of 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones to form 5-alkylidenecyclopentenediones has also been investigated. Compound **67** was prepared in moderate yield (45%) with an E:Z ratio of isomers of 12:1. The E-isomer was found to be thermodynamically more stable.⁴⁹ This reaction was very selective with regard to ring size and only five membered rings were obtained. The mechanism likely involves the coordination of the palladium to the

alkyne followed by 1,2-acyl migration and proteolytic cleavage of the σ -alkenylpalladium complex forming the alkylidene. The hydroxyl group is more likely to stabilize the positive charge left from the palladium induced 1,2-acyl migration (Scheme 34).

Scheme 34: Palladium Catalyzed Ring Expansion

2. Results and Discussion

In the following paragraphs the base mediated, transition metal mediated and catalyzed reactions of heteroatom tethered 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones and electrophilic ring expansions of 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones will be discussed. We envisioned a cyclization route to the indole nucleus and later ring expansion/cyclization of the 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones to form the 1,4-quinone instead of the previously synthesized 5-alkylidenecyclopentenediones. Several different methods for indole core and quinone formation were attempted. The methods tried were aimed at the formation of the indole nucleus and subsequent ring expansion to eventually form carbazolequinones.

The first set of these reactions, discussed above, included base mediated, copper mediated, copper and palladium catalyzed conditions. Electrophilic

methods were attempted to affect the ring expansion of the cyclobutenone moiety. The second set of reactions, discussed above, included *N*-iodosuccinimide mediated, *N*-chlorosuccinimide mediated and palladium catalyzed ring expansions.

2.1. Base Mediated Indole Formation

The BOC protected alkylation product **28a** was heated in dry *t*-BuOH at 83 °C in the presence of *t*-BuOK forming indole **68** in 20% yield. An explanation of this observation is that the base deprotonated the hydroxyl group of **28a** and induced a retro-alkylation. There was no evidence of the cyclobutenone moiety in the crude mixtures or in the purified products. It should be noted that the indole core was actually formed. No reaction occurred when *t*-BuOK or KH in NMP were used. *N*-acetyl derivative **46** was also reacted under the same conditions but yielded only unidentifiable products (Scheme 35). Based on this disappointing result no other base mediated indolizations were attempted.

Scheme 35: Base Mediated Indolization

2.2. Attempted Copper Mediated Indole Formation

Examples of an attempted copper mediated indolization reaction are shown in Scheme 36 and Scheme 37. The reaction conditions attempted for the *N*-BOC protected **28a** are summarized in Table 4. The yields were not corrected for the recovered starting material. In contrast to the reaction of the free amine shown in Scheme 25 *N*-BOC protection appears to inhibit the reaction. It seems that these reactions are simply thermal ring expansions of the cyclobutenone portion of the molecule. The copper mediated reactions were not attempted on the other *N*-BOC (**28b-28e**) or the *N*-acetyl **46** derivatives.

Scheme 36: Copper Mediated Reaction Scheme for *N*-BOC Protected 28a

Table 4: Copper Mediated Reaction Conditions for 28a

Temperature/Time	Cul (2 eq.)	33a	Recovered 28a
75 °C/24h	Yes	No Reaction	Not Calculated
85 °C/24h	Yes	8%	24%
100 °C/6h	Yes	11%	Not recovered
120 °C/1h	Yes	11%	32%
120 °C/1h	No	23%	18%

The Cul mediated reaction (Scheme 37) on the *N*-benzyl derivative **48** appears to undergo both thermal ring expansion leading to **35a** and metal mediated indolization-ring expansion-cyclization sequence leading to **69**. The formation of carbazolequinone **69** likely involves the copper coordinating with the alkyne followed by an intramolecular attack of the amine forming a metallo-indole intermediate. Subsequent acyl migration to form a metallocycle and then reductive elimination would form carbazolequinone **69**. Quinoline **35a** is likely formed from the thermal ring expansion of the cyclobutenone portion followed by the intramolecular iminium ion formation. It is likely that the benzyl group was removed from the iminium ion by a free iodide ion thus forming the quinoline **35a**. It should be noted that it is not clear whether the Cul affects any of the fore-mentioned ring expansion. This portion of the project was also abandoned since **48** was difficult to synthesize (Table 3, Scheme 22) and the reaction gave low yields.

Scheme 37: Copper Iodide Mediated Indolization for *N*-Benzyl Protected 48

2.3. Copper Acetate Catalyzed Indole Formation

Copper acetate catalyzed indole formation was attempted on derivatives **28a** and **46**. To our surprise the reaction on *N*-BOC protected compound **28a** cleaved the molecule into precursor alkyne and squaric acid derivative. The alkyne and squaric acid were recovered in 55% and 85%, respectively. On the other hand, *N*-acetyl compound **46** was cyclized to give the novel indole **70** in 72% yield (Scheme 38). The rearrangement of the squarate moiety is likely a consequence of acetic acid being liberated from the reaction. Acid catalyzed rearrangements of this type have been reported.^{50,19a} In the future this rearrangement could potentially be avoided by the addition of a mild scavenger base. This indolization reaction sequence was not attempted on other *N*-BOC (**28b-28e**) and *N*-benzyl (**48**) derivatives. The copper acetate catalyzed reactions were abandoned for the *N*-BOC case since the desired products, the indole moiety, were not obtained.

Scheme 38: Copper Acetate Catalyzed Indolization

2.4. Attempted Palladium Catalyzed Indole Formation or Ring Expansions

Reaction of **28a** and **48** with a number of palladium catalysts were examined.

The catalysts used include bis(triphenylphosphine)palladium dichloride and bis(benzonitrile)palladium dichloride. The free amine might be a better choice for this reaction, but we were unable to prepare this compound. The palladium catalyzed reactions were not attempted on the other *N*-BOC (**28b-28e**) or *N*-acetyl (**46**) derivatives. The palladium catalyzed reactions were abandoned since the desired products, the indole moiety, were not obtained.

2.5. *N*-Iodosuccinimide Mediated Ring Expansion

N-Iodosuccinimide mediated ring expansions were attempted on **28a**, **46** and **48**.

Two different reaction conditions were used for the **28a** and **46**. The first set of reaction conditions were tried on all three protecting group types. The compounds were dissolved in toluene and placed in thick walled flasks, sealed and heated to 150 °C in the presence of NIS. The second set of reaction

conditions were performed on the *N*-acetyl and *N*-BOC protected compounds in 1,2-DCE at 83 °C. In each case the expected products, iodoalkylenes, (Scheme 39) were not obtained. The products were unidentifiable.

Scheme 39: Attempted *N*-Iodosuccinimide Mediated Ring Expansion

2.6. *N*-Chlorosuccinimide Mediated Ring Expansion

The *N*-chlorosuccinimide ring expansions were attempted on **28a**, **46** and **48** (Scheme 40). The NCS reaction with **28a** was observed to cleave an isopropyl group and form dione **72** in 51% yield with alkyne still intact. The same result was observed for the reaction of **46** forming a 77% yield of **71**. Unidentifiable products were obtained from reaction of **48**. This type of rearrangement has been reported in the past for iodide mediated ring expansions (Scheme 41). The proposed mechanism is thought to proceed by the squarate hydroxyl group coordinating to the halide (structure **B**) followed by the loss of that hydroxyl moiety leaving a carbocationic intermediate **C**. Stabilization through the

resonance contribution of the alkoxy “trans” from the hydroxyl group could then allow the alkyl group on the alkoxy to be more easily removed. Removal of the alkyl group is likely to occur by halide attack thus forming the carbonyl and rearranged cyclobutenone **D**.⁴⁷ It is reasonable that the analogous reaction could occur using NCS. The NCS mediated ring expansions were not further examined using other *N*-BOC (**28b-28e**) protected derivatives.

Scheme 40: Attempted *N*-Chlorosuccinimide Mediated Ring Expansion

Scheme 41: Halide Mediated Cyclobutenone Rearrangement

3. Conclusions

These attempted indolization and ring expansion reactions were not further examined since the desired products were not obtained. The copper acetate catalyzed indolization of the *N*-acetyl derivative led to the preparation of novel 2-substituted indole. This methodology may be used in the future to prepare several other novel 2-substituted indoles. In the CuI mediated reactions with *N*-benzyl the project was dropped since the starting material was difficult to synthesize.

Part III

Synthesis of Novel Indoloquinones

1. Introduction

Indoloquinones are the core structure of many natural products including the mitosenes, isobatzellins, kinamycins and murrayaquinones.⁵¹ Many of these compounds are known to exhibit antitumor,⁵² antibacterial, antibiotic,⁵³ antileukemia, antifungal,⁵⁴ and myocardial contraction activity.⁵⁵ For example, mitomycin C (**73**) exhibits both antitumor and antibiotic activity,^{51,52} isobatzellin A (**74**) exhibits antileukemia and moderate antifungal activities⁵³ and murrayaquinone A (**75**) has been shown to induce myocardial contractions.⁵⁴ Kinamycin D (**76**) is strongly active against Gram-positive bacteria and less active against Gram-negative bacteria.^{52c}

Figure 3A: Indoloquinone Containing Natural Products

Mitomycin C (**73**)

Isobatzellin A (**74**)

Murrayaquinone A (**75**)

Kinamycin D (**76**)

Indoloquinones **79** and **82** have been isolated from mid-intestinal gland of muricid gastropod *Drupella fragum* collected off the Japanese coast. These two compounds are shown to exhibit moderate antimicrobial activity against several bacterial strains. Compounds **79** and **82** were synthesized for structural confirmation. Isovanillin **77** was used to synthesize **79** in 7 steps. **77** was nitrated in the 2-position and the resulting hydroxybenzaldehyde **77a** was acetylated **77b**. The aldehyde was then alkylated with nitromethane followed by dehydration to yield a dinitrostyrene followed by reductive indolization led to indole **78**. Deprotection and oxidation of **78** with salcomine under an atmosphere of oxygen gave indoloquinone **79** with a 6% overall yield. Indoloquinone **82** was synthesized in seven steps from 2,3-dimethoxybenzaldehyde **80** in a similar fashion in 12% overall yield (Scheme 42).⁵⁶

Scheme 42: Existing Synthesis of *Drupella fragum* Indoloquinones 79 and

82

2. Results and Discussion

We envisioned that the synthesis of indoles using aliphatic aminoalkynes (**83** and **87**) and a squarate derivative (**27**). The butyne starting materials were synthesized according to literature procedures.^{57,58} Alkylation of **27** with **83** and alkylation of **87** was obtained in excellent yield (85%). Cyclobutenone **89** was produced in 62% yield along with a number of inseparable products, probably rotomers of the carbamate (Scheme 43). As we observed previously addition of the squarate derivatives was the most consistent method for alkylation.

Scheme 43: Alkylation of **27** with **83** and **87**

Notes: a) -40 °C b) -78 °C

Upon thermal ring expansion of **88** and subsequent purification we were surprised to discover we had synthesized a novel 2,3-dihydroindoloquinone **91** in 51% yield (Scheme 44). During the separation the crude material changed color from yellow to green and finally to blue. Several other ring expansion conditions were attempted using xylenes (138 °C) and 1,2-DCE (83 °C). Reaction in xylenes led to faster conversion to **88** than compared to toluene but did not offer clean conversion to the indoloquinone (**91**). No reaction was observed using 1,2-DCE (83 °C) after 24 hours.

Scheme 44: Ring Expansion and Cyclization of 89 to 91

The proposed mechanism of the ring expansion, cyclization and oxidation is depicted in Scheme 45. The mechanism probably proceeds through the electrocyclic ring opening of **88** to give ketene **88a** followed by the 6-endo-dig cyclization forming intermediate **88b**. Subsequent hydrogen atom abstraction followed to give the diradical **88c** and later 1,4-quinone formation (**88d**). The next step probably was a Michael addition of the amine to the quinone followed by proton shift and tautomerization forming the hydroquinone **90**. Chromatography on silica gel probably caused the oxidation to indoloquinone **91**.

Scheme 45: Proposed Mechanism for the Tandem Expansion/Cyclization

of 89

Ammonium formate in the presence of Pd/C in refluxing MeOH has been reported to cleave the benzyl protecting groups.⁵⁹ Compound **91** was subjected to these reaction conditions but **93** was formed in a disappointing 28% yield (Scheme 46).

Scheme 46: Debenzylation of 91

DDQ has been used to oxidize dihydropyrroles to pyrroles⁶⁰ and dihydroindoles to indoles⁶¹. Compound **94** was produced in 65% yield *via* DDQ oxidation (Scheme 47).

Scheme 47: DDQ Oxidation of 91 to 94

A shorter synthesis of **79** was envisioned using a ring expansion methodology. The proposed synthetic steps are outlined in Scheme 48.

Scheme 48: Proposed Route for the Synthesis of 79

Ring expansion of **89** is somewhat problematic in toluene affording a number of inseparable products. However the ring expansion was cleaner in 1,2-DCE in a sealed tube at 100 °C giving **92** in 48% yield (Scheme 49).

Scheme 49: Ring Expansion of 89 to Quinone 92

Quinone **92** was deprotected with TFA and produced indoloquinone **91** in 51% yield (Scheme 50).

Scheme 50: Acidic Deprotection of 92 to 91

Future work should involve the synthesis of differently substituted alkynes to give 5 and 6 membered rings (Scheme 51).

Scheme 51: Proposed Future Research with Butyne Derivatives

3. Conclusions

In conclusion a novel route to indoloquinones has been discovered and may lead to the synthesis of a natural product, as well as several novel indoloquinones.

Part IV

Experimental

General Procedures. All NMR spectra were determined in CDCl_3 at 600 MHz (^1H NMR) and 150 MHz (^{13}C NMR) unless otherwise stated. The chemical shifts are expressed in δ values relative to Me_4Si (0.0, ^1H and ^{13}C) or CDCl_3 (77.0, ^{13}C) internal standards. ^1H - ^1H coupling constants are reported as calculated from spectra; thus, a slight difference between $J_{a,b}$ and $J_{b,a}$ is usually obtained. Results of APT (attached proton test) and DEPT- ^{13}C NMR experiments are shown in parentheses where, relative to CDCl_3 , (-) denotes CH_3 or CH and (+) denotes CH_2 or C . For ^1H NMR, the assignments are: q = quartet, t = triplet, d = doublet, s = singlet, br = broad, and m = multiplet. Multiplet refers to unresolved resonances from one or more protons having intractable ^1H - ^1H coupling constants.

Tetrahydrofuran (THF), toluene, dichloromethane, triethylamine, and diethyl ether were dried by passing through a steel column filled with activated alumina (8 x 14 mesh, Sorbent Technology) using argon pressure. Hexanes, EtOAc, and 1,2-dichloroethane (1,2-DCE) were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed in oven-dried glassware. *n*-BuLi concentrations were determined by titrating with either diphenyl acetic acid in THF or with tert-butanol, 1,10-phenanthroline in THF. Solvents were removed on a rotary evaporator at water aspirator pressure unless otherwise stated.

(4-Chloro-2-iodophenyl)-carbamic acid 1,1-dimethylethyl ester (37b). To a solution of 4-chloro-2-iodo-1-aminobenzene (**36b**) (1.44 g, 5.67 mmol) in THF (5 mL) sodium bis(trimethylsilyl)amide (NaHMDS) (1.0 M in THF, 12.5 mL, 12.5 mmol) was added *via* syringe over a 15 min period. A solution of BOC₂O (1.24 g, 5.67 mmol) in THF (5 mL) was added dropwise to the reaction mixture. The reaction mixture was then stirred at ambient temperature (24 h). The solvent was removed under reduced pressure and the residue was partitioned between HCl (aq., 0.1 M, 50 mL) and EtOAc (20 mL). The layers were separated and the aqueous layer was treated with sodium bicarbonate (saturated aq., 10 mL). The resulting aqueous phase was extracted with EtOAc (2 x 20 mL). The organic layers were combined, dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 95: 5) to give **37b** (1.63 g, 4.60 mmol, 81%) as an off-white solid. mp 42-45 °C; ¹H NMR (270 MHz) δ 8.00 (d, 1H, *J*=8.9 Hz), 7.72 (d, 1H, *J*=2.4 Hz), 7.28 (dd, 1H, *J*=8.9 and 2.4 Hz), 6.79 (br s, 1H), 1.53 (s, 9H); ¹³C NMR (67.5 MHz) δ 152.3 (+), 137.7 (-), 137.6 (+), 129.1 (-), 128.4 (+), 120.4 (-), 88.2 (+), 81.4 (+), 28.2 (-); IR (CCl₄) 3400, 2980, 1738, 1157 cm⁻¹.

(2-Iodo-5-methoxy-phenyl)-carbamic acid 1,1-dimethylethyl ester (37c).

Reaction of 2-iodo-5-methoxyaniline⁶² (**36c**) (409 mg, 1.64 mmol), sodium bis(trimethylsilyl)amide (1.0 M in THF, 3.60 mL, 3.60 mmol), and Boc₂O (355 mg, 1.63 mmol) in THF, as described above for **37b** (24 h), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2) **37c** (528 mg, 1.51 mmol, 92%) as

an off-white solid. mp 37-39 °C; ¹H NMR (270 MHz) 7.79 (d, 1H, *J*=2.8 Hz), 7.57 (d, 1H, *J*=8.9 Hz), 6.83 (br s, 1H), 6.40 (dd, 1H, *J*=8.9 and 2.9 Hz), 3.80 (s, 3H), 1.54 (s, 9H); ¹³C NMR (67.5 MHz) δ 160.7 (+), 152.4 (+), 139.6 (+), 138.7 (-), 111.7 (-), 105.1 (-), 81.1 (+), 55.4 (-), 28.3 (-); IR (CCl₄) 3396, 2981, 1734, 1158 cm⁻¹.

(2-Iodo-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester (37d).

Reaction of 2-iodo-5-methyl-1-aminobenzene⁶³ (**36d**) (897 mg, 3.84 mmol), sodium bis(trimethylsilyl)amide (1.0 M in THF, 4.2 ml, 8.4 mmol), and BOC₂O (846 mg, 3.88 mmol) in THF, as described for **37b** (24 h), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2) **37d** (1.122 g, 3.38 mmol, 88%) as an off-white solid. mp 79.5-82 °C; ¹H NMR (270 MHz) δ 7.91 (s, 1H), 7.59 (d, 1H, *J*=8.2 Hz), 6.79 (br s, 1H), 6.60 (dd, 1H, *J*=1.6 and 8.1 Hz), 2.31 (s, 3H), 1.54 (s, 9H); ¹³C NMR (67.5 MHz) δ 152.5 (+), 139.4 (+), 138.4 (+), 138.3 (-), 125.7 (-), 120.6 (-), 84.6 (+), 80.9 (+), 28.3 (-), 21.3 (-); IR (CCl₄) 3396, 2979, 2360 1736, 1160 cm⁻¹.

(4-Chloro-2-(trimethylsilylethynyl)phenyl)-carbamic acid 1,1-dimethylethyl

ester (38b). A mixture of **37b** (1.104 g, 3.12 mmol), bis(triphenylphosphine)palladium dichloride (22 mg, 0.031 mmol), copper iodide (7 mg, 0.037 mmol), and trimethylsilylethyne (470 μL, 3.30 mmol) in triethylamine (20 mL) was stirred at ambient temperature (24 h). The reaction was diluted with water (50 mL) and the resulting biphasic mixture was extracted with diethyl ether

(3 x 50 mL). The combined organic layers were washed with NH₄OH (10% aq., 25 mL), dried (MgSO₄), filtered, and the solvent were removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes: EtOAc, 95:5) to give **28b** (924 mg, 2.84 mmol, 91%) as a yellow solid. mp 72-76 °C; ¹H NMR (270 MHz) δ 8.08 (1H, *J*=9.1 Hz), 7.34 (d, 1H, *J*=2.6 Hz), 7.31 (br s, 1H), 7.25 (dd, 1H, *J*=8.9 and 2.4 Hz), 1.53 (s, 9H), 0.29 (s, 9H); ¹³C NMR (67.5 MHz) δ 152.1 (+), 138.8 (+), 130.7 (-), 129.8 (-), 126.6 (+), 118.3 (-), 112.3 (+), 103.4 (+), 99.0 (+), 80.9 (+), 28.2 (-), -0.3 (-); IR (CCl₄) 3400, 2977, 2152, 1737, 1157 cm⁻¹.

(5-Methoxy-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester (38c). Reaction of **37c** (504 mg, 1.44 mmol), bis(triphenylphosphine)palladium dichloride (54 mg, 0.077 mmol), copper iodide (14 mg, 0.074 mmol), and trimethylsilylethyne (230 μL, 1.59 mmol) in triethylamine (30 mL), as described for **38b** (ambient temperature, 24 h), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 95:5) **38c** (360 mg, 1.16 mmol, 80%) off-white solid. mp 39-41 °C; ¹H NMR δ 7.78 (s, 1H), 7.39 (s, 1H), 7.26 (d, 1H, *J*=9.0 Hz), 6.49 (dd, 1H, *J*=7.8 and 1.8 Hz), 3.82 (s, 3H), 1.53 (s, 9H), 0.28 (s, 9H); ¹³C NMR δ 160.9 (+), 152.3 (+), 141.9 (+), 132.2 (-), 108.9 (-), 103.0 (+), 102.1 (-), 100.8 (+), 100.5 (+), 80.6 (+), 55.4 (-), 28.3 (-), -0.1 (-); IR (CCl₄) 3395, 2963, 2347, 2144, 1734, 1157 cm⁻¹.

(5-Methyl-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl

ester (38d). Reaction of **37d** (450 mg, 1.36 mmol),

bis(triphenylphosphine)palladium dichloride (48 mg, 0.068 mmol), copper iodide

(16 mg, 0.084 mmol), and trimethylsilylethyne (200 μ L, 1.42 mmol) in

triethylamine (10 mL), as described for **38b** (ambient temperature, 24 h), gave

after workup and chromatography (SiO₂, hexanes: EtOAc, 95:5) **38d** (409 mg,

1.35 mmol, 100%) as a colorless oil. ¹H NMR (270 MHz) δ 7.96 (s, 1H), 7.40 (br

s, 1H), 7.15 (d, 1H, J =7.5 Hz), 6.75 (d, 1H, J =7.7 Hz), 2.34 (s, 3H), 1.53 (s, 9H),

0.28 (s, 9H); ¹³C NMR δ 152.4 (+), 140.5 (+), 140.1 (+), 131.0 (-), 122.8 (-), 117.7

(-), 108.1 (+), 101.3 (+), 100.8 (+), 80.5 (+), 28.3 (-), 22.0 (-), -0.1 (-); IR (CCl₄)

3396, 2977, 2348, 2148, 1736, 1159 cm⁻¹.

(4-Trimethylsilylethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester

(38e). Reaction of (4-iodo-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester⁶⁴

(37e) (1.96 g, 6.14 mmol), bis(triphenylphosphine)palladium dichloride (65 mg,

0.093 mmol), copper iodide (17 mg, 0.89 mmol), and trimethylsilylethyne (1.33

mL, 6.45 mmol) in triethylamine (20 mL), as described for **37b** (ambient

temperature, 24 h), gave after workup and chromatography (SiO₂,

hexanes:EtOAc, 1:1) **38e** (1.78 g, 6.14 mmol, 100%) as a brown solid. mp 59-61

°C; ¹H NMR (270 MHz) δ 9.39 (s, 1H), 8.24 (d, 1H, J =4.9 Hz), 7.21 (d, 1H, J =4.9

Hz), 7.12 (br s, 1H), 1.55 (s, 9H), 0.31 (s, 9H); ¹³C NMR (67.5 MHz) δ 151.8 (+),

142.9 (-), 139.9 (-), 135.8 (+), 124.2 (-), 118.2 (+), 106.9 (+), 97.6 (+), 81.4 (+),

28.1 (-), -0.4 (-); IR 3389, 2978, 2155, 1736, 1155 (CCl₄) cm⁻¹.

(4-Chloro-2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester (26b). To a solution of **38b** (924 mg, 2.85 mmol) in absolute ethanol:THF (1:1, 30 mL) was added a solution of NaOH⁶⁵ (1 M, 3 mL) and the resulting reaction mixture was allowed to stir (ambient temperature, 2 h). The solvents were removed at reduced pressure and the residue was suspended in water (10 mL) and extracted with diethyl ether (3 x 50 mL). The organic layers were combined, dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes: EtOAc, 9:1) to give **26b** (664 mg, 2.64 mmol, 92%) as an off-white solid. mp 61-63 °C; ¹H NMR (270 MHz) δ 8.13 (d, 1H, *J*=9.1 Hz), 7.39 (d, 1H, *J*=2.4 Hz), 7.29 (dd, 1H, *J*=9.1 and 2.6 Hz), 7.21 (br s, 1H), 3.52 (s, 1H), 1.53 (s, 9H); ¹³C NMR (67.5 MHz) δ 152.1 (+), 138.9 (+), 131.5 (-), 130.1 (-), 126.7 (+), 118.7 (-), 111.2 (+), 85.1 (+), 81.2 (+), 77.9 (+), 28.2 (-); IR (CCl₄) 3411, 3305, 2980, 2361, 1737, 1156 cm⁻¹.

(2-Ethynyl-5-methoxyphenyl)-carbamic acid 1,1-dimethylethyl ester (26c).

To a solution of **38c** (603 mg, 1.89 mmol) in methanol:THF:water (5:5:1, 11 mL) was added anhydrous potassium fluoride (334 mg, 5.75 mmol) and the resulting mixture was stirred (ambient temperature, 1 h). The reaction was diluted with water (50 mL) and extracted diethyl ether (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO₄), filtered, and the solvents were removed at reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 95:5) to give **26c** (366 mg, 1.59 mmol, 84%) as a colorless solid. mp around ambient temperature. ¹H NMR (270 MHz) δ

7.83 (d, 1H, $J=2.4$ Hz), 7.32 (d, 1H, $J=8.5$ Hz), 7.29 (br s, 1H), 6.51 (dd, 1H, $J=8.7$ and 2.6 Hz), 3.83 (s, 3H), 3.42 (s, 1H), 1.53 (s, 9H); ^{13}C NMR (67.5 MHz) δ 161.1 (+), 152.3 (+), 141.8 (+), 133.1 (-), 109.1 (-), 102.4 (-), 101.8 (+), 82.8 (+), 80.9 (+), 79.5 (+), 55.4 (-), 28.3 (-); IR 3407, 3309, 2980, 2360, 1734, 1157 cm^{-1} .

(2-Ethynyl-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester (26d).

Reaction of **38d** (400 mg, 1.32 mmol) with NaOH^{65} (1 M aq., 4 mL) in absolute ethanol:THF (1:1, 20 mL), as described for **26b** (ambient temp., 2 h), gave after workup and chromatography (SiO_2 , hexanes: EtOAc, 9:1) **26d** (241 mg, 1.05 mmol, 79%) as a yellow solid. mp 75-77 $^{\circ}\text{C}$ ^1H NMR (270 MHz) δ 8.01 (s, 1H), 7.31 (d, 1H, $J=7.9$ Hz), 7.24 (br s, 1H), 6.78 (d, 1H, $J=7.9$), 3.4 (s, 1H), 2.35 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (67.5 MHz) δ 152.4 (+), 140.7 (+), 140.1 (+), 131.9 (-), 122.9 (-), 117.9 (-), 106.9 (+), 83.4 (+), 80.7 (+), 79.5 (+), 28.3 (-), 21.9 (-); IR (CCl_4) 3408, 3309, 2978, 2926, 2347, 1735, 1157 cm^{-1} .

Alternative Procedure for: (2-Ethynyl-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester (26d).

Reaction of **38d** (389 mg, 1.29 mmol) with anhydrous fluoride dihydrate (226 mg, 3.89 mmol) in methanol:THF (1:1, 20 mL), as described for **26d** (ambient temperature, 1h), gave after workup and chromatography (SiO_2 , hexanes: EtOAc, 9:1) (217 mg, 0.94 mmol, 73%) a yellow solid.

(4-Ethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester (26e). Reaction of **38e** (1.78 g, 6.14 mmol) with potassium fluoride dihydrate (1.72 g, 18.3 mmol)

in methanol:THF (1:1, 15 mL), as described for **26c** (ambient temperature, 20 min), gave after workup and chromatography (SiO₂, hexanes: EtOAc, 1:1) **26e** (1.32 g, 6.08 mmol, 99%) as a brownish solid. mp 77-80 °C; ¹H NMR (270 MHz) δ 9.40 (s, 1H), 8.26 (d, 1H *J*=4.9 Hz), 7.28 (d, 1H, *J*=5.1 Hz), 7.09 (br s, 1H), 3.69 (s, 1H), 1.57 (s, 9H); ¹³C NMR (67.5 MHz) δ 151.9 (+), 143.0 (-), 140.4 (-), 136.0 (+), 125.2 (-), 117.3 (+), 88.1 (+), 88.0(+), 81.7 (+), 28.2 (-); IR (CCl₄) 3407, 3298, 2982, 2248, 1727, 1160 cm⁻¹.

Alternative Procedure for: (4-Ethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester (26e).

Reaction of **38e** (427 mg, 1.48 mmol) with NaOH⁶⁵ (1 M aq., 5 mL) in absolute ethanol:THF (1:1, 20 mL), as described for **26c** (ambient temp., 24 h), gave after workup and chromatography (SiO₂, hexanes: EtOAc, 7:3) (185 mg, 0.85 mmol, 61%) as a brownish solid.

[2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (28a). To a -5 °C cold solution of (2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester (**26a**)⁶⁶ (155 mg, 0.71 mmol) in THF (10 mL) was slowly added n-BuLi (1.6 M in hexanes, 1.1 mL, 1.8 mmol) via syringe. After 15 min, a -5 °C cold solution 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (**27**) (141 mg, 0.71 mmol) in THF (10 mL) was added to the dilithiated compound *via* a cannula. The resulting reaction mixture was stirred (ambient temperature, 30 min) followed by the

addition of water (40 mL). The biphasic mixture was extracted with diethyl ether (3 x 50 mL) and the combined organic layers were dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 8:2) to afford **28a** (189 mg, 0.45 mmol, 64%) as a brown oil and **26a** (20 mg, 0.09 mmol). ¹H NMR (270 MHz) δ 8.14 (d, 1H, *J*=8.3 Hz), 7.40 (dd, 1H, *J*=7.7 and 1.4 Hz), 7.32 (dt, 1H, *J*=8.7 and 1.6 Hz), 7.14 (br s, 1H), 6.95 (dt, 1H, *J*=7.5 and 1.0 Hz), 5.02 (heptet, 1H, *J*=6.1 Hz), 4.92 (heptet, 1H, *J*=6.1 Hz), 3.07 (br s, 1H), 1.53 (s, 9H), 1.48 (d, 3H, *J*=6.3 Hz), 1.47 (d, 3H, *J*=6.1 Hz), 1.33 (d, 3H, *J*=6.1 Hz), 1.32 (d, 3H, *J*=6.1 Hz); ¹³C NMR (67.5 MHz) δ 180.4 (+), 164.1 (+), 152.4 (+), 139.7 (+), 133.8 (+), 132.2 (-), 130.1 (-), 122.0 (-), 117.8 (-), 109.9 (+), 90.2 (+), 83.8 (+), 80.9 (+), 78.9 (+), 78.1 (-), 74.3 (-), 28.3 (-), 22.7 (-), 22.6 (-), 22.5 (-); IR (CCl₄) 3402, 2980, 2933, 1734, 1158 cm⁻¹.

Alternative Procedure for: [2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (28a).

4-Ethynyl-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone⁶⁹ (**39**) (272 mg, 1.21 mmol), bis(triphenylphosphine)palladium dichloride (45 mg, 0.063 mmol), copper iodide (238 mg, 1.25 mmol) were slurried in 30 mL NEt₃. **37a** (394 mg, 1.23 mmol) was added after five minutes and the reaction was allowed to stir. After 24 hours the reaction was diluted with 50 mL water and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with 20 mL 10% NH₄OH, dried (MgSO₄), filtered, and the solvents were removed under reduced

pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 8:2) to afford **28a** (189 mg, 0.35 mmol, 36%) as a brown oil and **37a** (155 mg, 0.48 mmol, 61%).

[4-Chloro-2-(1-hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (28b). Reaction of **26b** (250 mg, 0.99 mmol), *n*-BuLi (2.65 M in hexanes, 0.93 mL, 2.4 mmol), and 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (**27**) (198 mg, 1.00 mmol) in THF (20 mL total), as described for **28a** (30 min), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2), **28b** (349 mg, 0.77 mmol, 78%) as a yellow solid. mp 123-125 °C; ¹H NMR (270 MHz) δ 8.08 (d, 1H, *J*=8.9 Hz), 7.34 (d, 1H, *J*=2.4 Hz), 7.25 (dd, 1H, *J*=2.6 and 8.9 Hz), 7.15 (br s, 1H), 5.02 (heptet, 1H, *J*=6.1 Hz), 4.89 (heptet, 1H, *J*=6.1 Hz), 3.74 (br s, 1H), 1.53 (s, 9H), 1.48 (d, 3H, *J*=6.1 Hz), 1.47 (d, 3H, *J*=6.1 Hz); 1.32 (d, 6H, *J*=6.1 Hz); ¹³C NMR (67.5 MHz) δ 180.6 (+), 164.2 (+), 152.3 (+), 138.4 (+), 133.8 (+), 131.4 (-), 130.1 (-), 126.8 (+), 119.1 (-), 111.4 (+), 91.3 (+), 82.4 (+), 81.2 (+), 78.6 (+), 78.2 (-), 74.3 (-), 28.2 (-), 22.7 (-), 22.6 (-), 22.5 (-); IR (CCl₄) 3424, 2968, 2355, 1734, 1157 cm⁻¹.

[2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester (28c). Reaction of **26c** (192 mg, 0.80 mmol), *n*-BuLi (1.4 M in hexanes, 1.43 mL, 2.01 mmol), and 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (**27**) (106 mg, 0.81 mmol) in THF

(25 mL total) as described for **28a** (30 min), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2) an inseparable mixture of **28c** and 4-butyl-4-hydroxy-2,3-di(1-methylethoxy)-2-cyclobuten-1-one (215 mg, 4:1 ratio). Spectral data from the mixture: ¹H NMR (270 MHz) δ 7.80 (d, 1H, *J*=2.2 Hz), 7.28 (d, 1H, *J*=8.3 Hz), 7.17 (br s, 1H), 6.50 (dd, 1H, *J*=8.5 and 2.6 Hz), 5.02 (heptet, 1H, *J*=6.1 Hz), 4.90 (heptet, 1H, *J*=6.3 Hz), 3.82 (s, 3H), 3.21 (br s, 1H), 1.53 (s, 9H), 1.48 (d, 3H, *J*=6.3 Hz), 1.46 (d, 3H, *J*=6.1 Hz), 1.32 (d, 3H, *J*=6.1 Hz), 1.31 (d, 3H, *J*=6.1 Hz); ¹³C NMR (67.5 MHz) δ 180.7 (+), 164.3 (+), 161.1 (+), 152.3 (+), 141.3 (+), 133.7 (+), 133.1 (-), 109.1 (-), 102.5 (-), 101.9 (+), 89.1 (-), 83.9 (+), 80.9 (+), 78.9 (+), 74.2 (-), 28.3 (-), 22.7 (-), 22.6 (-), 22.5 (-), 22.3 (-); IR (CCl₄) 3565, 2989, 2942, 1731, 1161 cm⁻¹.

Alternative Procedure for: [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester (28c). 4-Ethynyl-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone⁶⁹ (**39**) (581 mg, 2.59 mmol), bis(triphenylphosphine)palladium dichloride (91 mg, 0.013 mmol), copper iodide (496 mg, 2.61 mmol) were slurried in 30 mL NEt₃. (2-Iodo-5-methoxy-phenyl)-carbamic acid 1,1-dimethylethyl ester (**37c**) (912 mg, 2.61 mmol) was added after five minutes and the reaction was allowed to stir. After 20 hours the reaction was diluted with 50 mL water and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with 20 mL 10% NH₄OH, dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO₂,

hexanes:EtOAc, 8:2) to afford **28c** (747 mg, 1.68 mmol, 65%) as fluffy orange yellow solid. mp 38 – 42 °C. ¹H NMR (270 MHz) δ 7.76 (d, 1H, J = 2.4 Hz), 7.26 (d, 1H, J = 8.7 Hz), 6.48 (dd, 1H, J = 8.7 and 2.6 Hz), 5.03 (heptet, 1H, J = 6.1 Hz), 4.88 (heptet, 1H, J = 6.1 Hz), 3.94 (br. s, 1H), 3.82 (s, 3H), 1.53 (s, 9H), 1.47 (overlapping d, 3H, J = 6.2 Hz), 1.46 (overlapping d, 3H, J = 6.1 Hz), 1.29 (d, 6H, J = 6.1 Hz); ¹³C NMR (67.5 MHz) δ 181.3 (+), 164.8 (+), 160.8 (+), 152.2 (+), 141.1 (+), 133.3 (+), 132.9 (-), 108.9 (-), 102.5 (-), 101.9 (+), 89.1 (+), 83.6 (+), 80.7 (+), 78.6 (+), 77.8 (-), 73.9 (-), 55.1 (-), 28.1 (-), 22.5 (-), 22.4 (-), 22.3 (-); IR (neat) 3398 (br.), 2979, 2213, 1774, 1730 cm⁻¹.

[2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methylphenyl]-carbamic acid 1,1-dimethylethyl ester (28d). Reaction of **11c** (241 mg, 1.05 mmol), *n*-BuLi (1.6 M in hexanes, 1.64 mL, 2.62 mmol), and 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (**27**) (207 mg, 1.04 mmol) in THF (30 mL total), as described for **28a** (30 min), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2) **28d** (222 mg, 0.52 mmol, 50%) as a yellow oil and **26c** (70 mg, 0.30 mmol). ¹H NMR (270 MHz) δ 7.98 (s, 1H), 7.26 (d, 1H, J=7.9 Hz), 7.12 (br s, 1H), 6.77 (d, 1H, J=7.9 Hz), 5.02 (heptet, 1H, J=6.1 Hz), 4.90 (heptet, 1H, J=6.1 Hz), 3.16 (br s, 1H), 2.34 (s, 3H), 1.53 (s, 9H), 1.48 (d, 3H, J=6.3 Hz), 1.46 (d, 3H, J=6.1 Hz) 1.32 (d, 3H, J=6.1 Hz), 1.31 (d, 3H, J=6.1 Hz); ¹³C NMR (67.5 MHz) δ 180.3 (+), 164.1 (+), 152.4 (+), 140.9 (+), 139.6 (+), 133.9 (+), 131.9 (-), 123.0 (-), 118.3 (-), 106.9 (+), 89.6 (+), 84.1 (+),

80.8 (+), 78.9 (+), 78.0 (-), 74.3 (-), 28.3 (-), 22.7 (-), 22.6 (-), 22.5 (-), 21.9 (-); IR (CCl₄) 3424, 2978, 1731, 1637, 1161 cm⁻¹.

[4-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-pyridin-3-yl]-carbamic acid 1,1-dimethylethyl ester (28e). Reaction of **26e** (1.05 g, 4.81 mmol), *n*-BuLi (2.89 M in hexanes, 4.16 mL, 12.04 mmol), and 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (**27**) (0.96 g, 4.83 mmol) in THF (40 mL total), as described for **28a**, gave after workup and chromatography (SiO₂, hexanes:EtOAc, 1:1), **28e** (1.14 g, 2.74 mmol, 57%) as a brown oil. ¹H NMR (270 MHz) δ 9.40 (s, 1H), 8.24 (d, 1H, *J*=4.9 Hz), 7.24 (d, 1H, *J*=4.9 Hz), 6.99 (br s, 1H), 5.02 (heptet, 1H, *J*=6.1 Hz), 4.91 (heptet, 1H, *J*=6.1 Hz), 4.57 (br s, 1H), 1.53 (s, 9H), 1.47 (d, 3H, *J*=6.3 Hz), 1.46 (d, 3H, *J*=6.1 Hz), 1.32 (d, 3H, *J*=6.1 Hz), 1.31 (d, 3H, *J*=6.1 Hz); ¹³C NMR (67.5 MHz) δ 180.0 (+), 164.0 (+), 151.8 (+), 142.3 (-), 139.9 (-), 139.8 (-), 135.7 (+), 133.8 (+), 125.3 (-), 118.0 (+), 95.5 (+), 81.6 (+), 80.5 (+), 78.5 (+), 78.1 (-), 78.0 (-), 74.3 (-), 74.2 (-), 28.1 (-), 22.6 (-), 22.5 (-), 22.4 (-); IR (CCl₄) 3405 (br.), 2978, 2360, 1737, 1158 cm⁻¹.

[2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (33a). A solution of **28a** (325 mg, 0.78 mmol) in toluene (20 mL) was heated at reflux overnight. The reaction was cooled to ambient temperature and the solvent was removed under reduced pressure. The crude residue was purified by chromatography (SiO₂, hexanes:EtOAc, 95:5) to give **33a** (265 mg, 0.64 mmol, 82%) as an orange solid. mp 93-

96 °C; ^1H NMR (270 MHz) δ 7.91 (dd, 1H, $J=7.9$ and 1.6 Hz), 7.80 (d, 1H, $J=8.1$ Hz), 7.44 (s, 1H), overlapping 7.40 (t, 1H, $J=8.7$ Hz), 7.13 (t, 1H, $J=7.5$ Hz), 6.54 (br s, 1H), 5.59 (m, 2H), 1.51 (s, 9H), 1.40 (d, 6H, $J=6.3$ Hz), 1.37 (d, 6H, $J=6.1$ Hz); ^{13}C NMR (67.5 MHz) δ 185.9 (+), 184.4 (+), 152.8 (+), 151.9 (+), 149.4 (+), 137.8 (+), 131.7 (-), 131.5 (-), 130.8 (-), 127.3 (+), 124.2 (+), 123.4 (-), 122.2 (-), 80.9 (+), 74.9 (-), 74.8 (-), 28.2 (-), 22.9 (-), 22.6 (-); IR (CDCl_3) 3326 (br), 2980, 2933, 1733, 1156 cm^{-1} .

[4-Chloro-2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (33b). Reaction of **28b** (452 mg, 1.00 mmol) in toluene (20 mL), as described for **33a**, gave after workup and chromatography (SiO_2 , hexanes:EtOAc, 8:2) **33b** (307 mg, 0.68 mmol, 68%) as a yellow solid. mp 57-62 °C; ^1H NMR (270 MHz) δ 7.93 (d, 1H, $J=2.4$ Hz), 7.79 (d, 1H, $J=8.5$ Hz), 7.34 (dd, 1H, $J=8.7$ and 2.4 Hz), 7.32 (s, 1H), 6.48 (br s, 1H), 5.59 (m, 2H), 1.51 (s, 9H), 1.40 (d, 6H, $J=5.5$ Hz), 1.38 (d, 6H, $J=5.9$ Hz); ^{13}C NMR δ 185.4 (+), 184.0 (+), 152.7 (+), 152.6 (+), 149.8 (+), 136.3 (+), 131.2 (-), 131.0 (-), 128.9 (+), 128.7 (-), 128.5 (+), 81.3 (+), 75.2 (-), 75.1 (-), 65.8 (+), 28.2 (-), 23.0 (-), 23.0 (-), 15.2 (-); IR (CDCl_3) 3149, 2982, 2254, 1727, 1160 cm^{-1} .

[2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester (33c). Reaction of a 4:1 mixture of **28c**:4-butyl-4-hydroxy-2,3-di(1-methylethoxy)-2-cyclobuten-1-one (215 mg) in toluene (20 mL), as described for **33a** (110 °C, 18h), gave after was

chromatography (SiO₂, hexanes:EtOAc, 8:2) **33c** (84 mg, 0.19 mmol, 39% from **28c**) as an orange-yellow solid. mp 99-102 °C; ¹H NMR (270 MHz) δ 8.15 (d, 1H, *J*=9.0 Hz), 7.48 (br s, 1H), 7.38 (s, 1H), 6.79 (s, 2H), 6.68 (dd, 1H, *J*=8.4 and 2.4 Hz), 5.53 (m, 2H), 3.85 (s, 3H), 1.52 (s, 9H), 1.39 (d, 6H, *J*=6.0 Hz), 1.38 (d, 6H, *J*=6.0 Hz); ¹³C NMR δ 186.8 (+), 185.0 (+), 162.9 (+), 152.5 (+), 151.4 (+), 148.4 (+), 140.3 (+), 133.8 (-), 130.5 (-), 124.5 (+), 116.0 (+), 110.1 (-), 106.3 (+), 81.1 (+), 74.8 (-), 74.7 (-), 55.4 (-), 28.2 (+), 22.9 (+); IR (CCl₄) 3445, 2980, 2933, 1733, 1670, 1156 cm⁻¹.

[2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-methylidene)-5-methyl-phenyl]-carbamic acid 1,1-dimethylethyl ester (33d). Reaction of **28d** (59 mg, 0.14 mmol) in toluene (20 mL), as described for **33a** (reflux, overnight), gave after chromatography (SiO₂, hexanes:EtOAc, 8:2) **33d** (49 mg, 0.11 mmol, 83%) as a colorless oil. ¹H NMR (270 MHz) δ 7.89 (d, 1H, *J*=8.1 Hz), 7.65 (s, 1H), 7.42 (s, 1H), 6.95 (d, 1H, *J*=7.1 Hz), 6.56 (br s, 1H), 5.57 (m, 2H), 2.37 (s, 3H), 1.51 (s, 9H), 1.40 (d, 6H, *J*=6.1 Hz), 1.37 (d, 6H, *J*=6.1 Hz); ¹³C NMR (67.5MHz) δ 186.3 (+), 184.7 (+), 152.8 (+), 151.8 (+), 149.1 (+), 142.8 (+), 137.9 (+), 131.8 (-), 130.8 (-), 126.4 (+), 124.5 (-), 122.5 (-), 121.3 (+), 80.9 (+), 74.9 (-), 74.8 (-), 29.7 (+), 28.3 (-), 23.0 (-), 21.8 (-); IR (CCl₄) 3437, 2980, 2360, 1734, 1672, 1157 cm⁻¹.

[4-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-3-pyridinyl]-carbamic acid 1,1-dimethylethyl ester (33e). Reaction of **28e** (107 mg, 0.26

mmol) in refluxing 1,2-dichloroethane⁷⁰ (20 mL) 18 h. The reaction was cooled to room temperature and the solvent was removed. The resulting residue was chromatographed (SiO₂, hexanes:EtOAc, 6:4) **33e** (83 mg, 0.20 mmol, 78%) as a brown solid. mp 117-119 °C; ¹H NMR δ 8.99 (s, 1H), 8.40 (d, 1H, *J*=5.3 Hz), 7.66 (d, 1H, *J*=5.2 Hz), 7.30 (s, 1H), 6.45 (br s, 1H), 5.61 (m, 2H), 1.51 (s, 9H), 1.41 (d, 6H, *J*=6.3 Hz), 1.38 (d, 6H, *J*=6.3 Hz); ¹³C NMR δ 184.5 (+), 183.6 (+), 153.1 (+), 152.6 (+), 150.8 (+), 144.8 (-), 144.3 (-), 133.1 (+), 132.3 (+), 130.7 (+), 127.3 (-), 124.2 (-), 81.6 (+), 75.5 (-), 75.4 (-), 28.1 (-), 23.0 (-); IR (CCl₄) 3000, 2960, 1740, 1690, 1160 cm⁻¹.

2,3-Di(1-methylethoxy)cyclopenta[*b*]quinolin-1-one (34a). A solution of **33a** (169 mg, 0.41 mmol) in EtOAc:HCl⁶⁷ (1:1, 3 M aq. HCl, 20 mL) was stirred at ambient temperature (6 d). The solvents were removed under reduced pressure and the resulting residue was suspended in water (20 mL) and extracted with diethyl ether (100 mL). The organic layers were washed with NaHCO₃ (aq. saturated 25 mL), dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 8:2) to give **34a** (112 mg, 0.27 mmol, 66%) as a yellow-orange solid. mp 59-61 °C; ¹H NMR (270 MHz) δ 8.05 (d, 1H, *J*=8.3 Hz), 7.79 (s, 1H), 7.71 (dd, 1H, *J*=7.9 and 1.4 Hz), 7.62 (dt, 1H, *J*=7.1 and 1.4 Hz), 7.42 (dt, 1H, *J*=8.1 and 1.2 Hz), 5.68 (heptet, 1H, *J*=6.3 Hz), 5.26 (heptet, 1H, *J*=6.1 Hz), 1.50 (d, 6H, *J*=6.1 Hz), 1.35 (d, 6H, *J*=6.1 Hz); ¹³C NMR (67.5 MHz) δ 187.2 (+), 158.0 (+), 156.8 (+), 149.2 (+), 138.2 (+), 130.6 (-), 129.8 (-), 129.7 (-), 127.7 (+), 126.8

(-), 126.3 (-), 123.7 (+), 76.5 (-), 73.8 (-), 22.9 (-), 22.8 (-); IR (CCl₄) 3436, 2978, 1695, 1102 cm⁻¹.

Alternative procedure for: 2,3-Di(1-methylethoxy)cyclopenta[*b*]quinolin-1-one (34a). A solution of **33a** (566 mg, 1.36 mmol) in CH₂Cl₂ (20 mL) was treated with 2.5 mL TFA⁶⁸ (trifluoroacetic acid) at 0 °C for 30 minutes. The reaction was then warmed to 50 °C for 3h. The reaction was cooled to room temperature and the solvents were removed under reduced pressure. The resulting residue was neutralized with 30 mL aqueous saturated NaHCO₃ and extracted with 3X 30 mL portions of CH₂Cl₂. The organic layer was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 8:2) to give **33a** (298 mg, 1.00 mmol, 74%) as a yellow-orange solid.

7-Chloro-2,3-di(1-methylethoxy)cyclopenta[*b*]quinolin-1-one (34b). Reaction of **33b** (163 mg, 0.44 mmol) in EtOAc:HCl⁶⁷ (1:1, 3 M aq. HCl, 30 mL), as described for **34a** (ambient temperature, 3 d), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2), **34b** (71 mg, 0.24 mmol, 54%) as an orange solid. mp 104-106 °C; ¹H NMR (270 MHz) δ 7.99 (d, 1H, *J*=8.9 Hz), 7.69 (s, 1H), 7.68 (s, 1H) overlapping 7.61 (d, 1H, *J*=2.3 Hz), 7.55 (dd, 1H, *J*=8.7 and 2.3 Hz), 5.66 (heptet, 1H, *J*=6.1 Hz), 5.28 (heptet, 1H, *J*=6.1 Hz), 1.51 (d, 6H, *J*=6.3 Hz), 1.36 (d, 6H, *J*=6.3 Hz); ¹³C NMR (67.5 MHz) δ 186.5 (+), 158.5 (+), 156.7 (+), 147.5 (+), 138.4 (+), 132.4 (+), 131.0 (-), 128.6 (-), 128.5 (-), 125.2

(-), 124.6 (+), 75.3 (-), 73.9 (-), 22.9 (-), 22.8 (-); IR (CCl₄) 3410, 2982, 2931, 2360, 1700, 1101 cm⁻¹.

2,3-Di(1-methylethoxy)-6-methoxycyclopenta[*b*]quinolin-1-one (34c).

Reaction of **33c** (154 mg, 0.35 mmol) in EtOAc:HCl⁶⁷ (4:3, 3 M aq. HCl, 35 mL), as described for **34a** (ambient temperature, 2 d), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2) **34c** (88 mg, 0.27 mmol, 78%) as a yellow oil. ¹H NMR (270 MHz) δ 7.73 (s, 1H), 7.60 (d, 1H, *J*=8.7 Hz), 7.48 (d, 1H, *J*=2.6 Hz), 7.05 (dd, 1H, *J*=8.7 and 2.6 Hz), 5.62 (heptet, 1H, *J*=6.1 Hz), 5.23 (heptet, 1H, *J*=6.1 Hz), 3.92 (s, 3H), 1.49 (d, 6H, *J*=6.1 Hz), 1.34 (d, 6H, *J*=6.1 Hz); ¹³C NMR (67.5 MHz) δ 187.6 (+), 161.6 (+), 159.2 (+), 156.1 (+), 151.0 (+), 137.1 (+), 130.6 (-), 126.1 (-), 121.9 (+), 121.2 (+), 117.9 (-), 109.9 (-), 74.8 (-), 73.7 (-), 55.5 (-), 22.8 (-), 22.7 (-); IR (CCl₄) 2980, 2932, 2359, 1701, 1108 cm⁻¹.

2,3-Di(1-methylethoxy)-6-methylcyclopenta[*b*]quinolin-1-one (34d).

Reaction of **33d** (185 mg, 0.43 mmol) in EtOAc:HCl⁶⁷ (3:2, 3 M aq. HCl, 25 mL), as described for **34a** (ambient temperature, 2 d), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2) **34d** (94 mg, 0.30 mmol, 70 %) as a yellow-orange solid. mp 78-80 °C; ¹H NMR (270 MHz) δ 7.85 (s, 1H), 7.75 (s, 1H), 7.60 (d, 1H, *J*=8.1 Hz), 7.26 (dd, 1H, *J*=7.5 and 1.4 Hz), 5.67 (heptet, 1H, *J*=6.1 Hz), 5.22 (heptet, 1H, *J*=6.1 Hz), 2.46 (s, 3H), 1.49 (d, 6H, *J*=6.1 Hz), 1.34 (d, 6H, *J*=6.1 Hz); ¹³C NMR (67.5 MHz) δ 187.3 (+), 158.5 (+), 156.5 (+), 149.2 (+), 141.2 (+), 137.8 (+), 129.5 (-), 129.4 (-), 128.5 (-), 126.2 (-), 125.3 (+), 122.8

(+), 74.9 (-), 73.7 (-), 22.9 (-), 22.7 (-), 21.7 (-); IR (CCl₄) 3000, 2950, 1715, 1645, 1155 cm⁻¹.

2,3-Di(1-methylethoxy)-6-aza-cyclopenta[*b*]quinolin-1-one (34e). To a 0 °C cold solution of **33e** (273 mg, 0.66 mmol) in CH₂Cl₂ (15 mL) was slowly added trifluoroacetic acid⁶⁸ (1.0 mL, 5.93 mmol). The reaction mixture was allowed to stir (0 °C, 4 h, then reflux, 1 h). The solvent was removed under reduced pressure and the residue was suspended in NaHCO₃ (aq. saturated, 10 mL). The suspension was extracted with CH₂Cl₂ (100 mL) and the combined organic layers were, dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 1:1) to give **34e** (168 mg, 0.56 mmol, 86%) as an orange solid. mp 73-76 °C; ¹H NMR (270 MHz) δ 9.37 (s, 1H), 8.55 (d, 1H, *J*=5.3 Hz), 7.74 (s, 1H), 7.55 (d, 1H, *J*=5.2 Hz), 5.71 (heptet, 1H, *J*=6.1 Hz), 5.32 (heptet, 1H, *J*=6.1 Hz), 1.51 (d, 6H, *J*=6.1 Hz), 1.36 (d, 6H, *J*=6.1 Hz); ¹³C NMR δ 185.6 (+), 159.6 (+), 156.9 (+), 152.9 (-), 145.4 (-), 143.9 (+), 139.8 (+), 131.9 (+), 127.7 (+), 124.2 (-), 121.9 (-), 75.6 (-), 74.1 (-), 22.9 (-), 22.8 (-); IR (CHCl₃) 2985, 2348, 2254, 1704, 1094 cm⁻¹.

2,3-Di(1-methylethoxy)cyclopenta[*b*]quinolin-1-ol (35a). To a 0 °C cold solution of **34a** (96 mg, 0.32 mmol) in THF (10 mL) was added NaBH₄ (130 mg, 3.44 mmol) and the resulting mixture was allowed to stir (3 h). Methanol (1.55 mL, 35.51 mmol) was added and the mixture was diluted with water (20 mL) and

extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 8:2) to afford **35a** (81 mg, 0.27 mmol, 84%) as a pale yellow oil. ¹H NMR δ 7.93 (d, 1H, *J*=7.8), 7.78 (s, 1H), 7.53 (m, 2H), 7.32 (dt, 1H, *J*=1.2, 7.8 Hz), 5.29 (heptet, 1H, *J*=5.4 Hz), 5.13 (heptet, 1H, *J*=6.0 Hz), 5.02 (br s, 1H), 2.75 (br s, 1H), 1.36 (d, 3H, *J*=5.4 Hz), 1.34 (d, 3H, *J*=6.0 Hz), 1.33 (d, 3H, *J*=6.0 Hz), 1.31 (d, 3H, *J*=6.0 Hz); ¹³C NMR δ 159.8 (+), 151.5 (+), 148.2 (+), 133.8 (+), 131.1 (+), 128.7 (-), 128.5 (-), 128.1 (-), 127.9 (-), 126.4 (+), 124.8 (-), 72.9 (-), 72.3 (-), 68.7 (-), 22.91 (-), 22.90 (-), 22.64 (-), 22.61 (-); IR (CCl₄) 3277, 3061, 2979, 2935, 2360, 1317, 1104 cm⁻¹.

7-Chloro-2,3-di(1-methylethoxy)cyclopenta[*b*]quinolin-1-ol (35b). Reaction of **34b** (80 mg, 0.27 mmol) with NaBH₄ (106 mg, 2.80 mmol), and methanol (1.30 mL, 29.58 mmol) in THF (10 mL), as described for **35a** (3 h), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2) **35b** (55 mg, 0.18 mmol, 68%) as a light yellow oil. ¹H NMR δ 7.83 (d, 1H, *J*=9.0 Hz), 7.58 (s, 1H), 7.51 (d, 1H, *J*=1.8 Hz), 7.47 (dd, 1H, *J*=8.4 and 2.4 Hz), 5.24 (heptet, 1H, *J*=6.0 Hz), 5.15 (heptet, 1H, *J*=6.0 Hz), 5.01 (br s, 1H), 2.75 (br s, 1H), 1.40 (d, 3H, *J*=6.0 Hz), 1.36 (d, 3H, *J*=6.0 Hz), 1.35 (d, 3H, *J*=6.0 Hz), 1.34 (d, 3H, *J*=6.0 Hz); ¹³C NMR δ 160.3 (+), 152.2 (+), 146.8 (+), 133.8 (+), 132.2 (+), 130.4 (-), 130.1 (-), 129.6 (+), 127.3 (-), 127.2 (-), 126.9 (+), 73.4 (-), 72.7 (-), 68.8 (-), 23.17 (-), 23.15 (-), 22.87 (-), 22.83 (-); IR (CHCl₃) 3366 (br.), 2976, 1313, 1104.

2,3-Di(1-methylethoxy)-6-methoxycyclopenta[*b*]quinolin-1-ol (35c). Reaction of **34c** (61 mg, 0.19 mmol), NaBH₄ (80 mg, 2.11 mmol), and methanol (0.91 mL, 20.95 mmol) in THF (10 mL), as described for **35a** (18h), gave after workup and chromatography (SiO₂, hexanes:EtOAc, 8:2) **35c** (43 mg, 0.13 mmol, 70%) as a yellow oil. ¹H NMR (270 MHz) δ 7.78 (s, 1H), 7.56 (d, 1H, *J*=8.9 Hz), 7.40 (d, 1H, *J*=2.4 Hz), 7.03 (dd, 1H, *J*=8.7 and 2.6 Hz), 5.34 (heptet, 1H, *J*=5.7 Hz), 5.12 (heptet, 1H, *J*=5.9 Hz), 5.06 (d, 1H, *J*=6.9 Hz), 3.92 (s, 3H), 1.38 (m, 12H); ¹³C NMR (67.5 MHz) δ 160.2 (+), 159.9 (+), 151.1 (+), 149.7 (+), 133.9 (+), 128.8 (+), 127.9 (-), 120.9 (+), 116.6 (-), 107.9 (-), 72.9 (-), 72.3 (-), 68.6 (-), 55.4 (-), 22.9 (-), 22.6 (-); IR (CCl₄) 3412, 2977, 2931, 1105 cm⁻¹.

2,3-Di(1-methylethoxy)-6-methylcyclopenta[*b*]quinolin-1-ol (35d). Reaction of **34d** (94 mg, 0.30 mmol), NaBH₄ (118 mg, 2.80 mmol), and methanol (1.44 mL, 33.2 mmol) in THF (10 mL), as described for **35a** (18h), gave after workup and chromatography (SiO₂, hexanes: EtOAc, 8:2) **35d** (66 mg, 0.21 mmol, 70%) as a faint yellow oil. ¹H NMR δ 7.79 (s, 2H), 7.58 (d, 1H, *J*=7.9 Hz), 7.21 (d, 1H, *J*=9.1 Hz), 5.39 (heptet, 1H, *J*=6.1 Hz), 5.15, (heptet, 1H, *J*=6.1 Hz), 5.04 (d, *J*=5.1 Hz), 2.51 (s, 3H), 1.38 (m, 12H); ¹³C NMR δ 159.6 (+), 151.4 (+), 148.1 (+), 138.8 (+), 133.7 (+), 130.2 (+), 127.9 (-), 127.7 (-), 127.5 (-), 126.6 (-), 124.1 (+), 72.8 (-), 72.2 (-), 68.5 (-), 22.9 (-), 22.6 (-), 21.6 (-); IR (CCl₄) 3400, 2978, 2933, 1105 cm⁻¹.

2,3-Di(1-methylethoxy)-6-azacyclopenta[*b*]quinolin-1-ol (35e). To a 0 °C cold solution of **34e** (414 mg, 3.36 mmol) in THF:MeOH (1:1, 10 mL) was added NaBH₄ (110 mg, 2.91 mmol). The reaction was stirred for 10 min at 0 °C and subsequently quenched with water (20 mL). The mixture was quickly extracted with ethyl acetate (3 x 50 mL), and the combined organic layers were dried (Na₂SO₄), filtered, and the solvents were removed under reduced pressure. The residue was purified by chromatography (SiO₂, hexanes:EtOAc, 3:7) to give **35e** (212 mg, 0.71 mmol, 51%) as a white solid which quickly turned yellow. Tentative NMR assignments from a rapidly decomposing compound. ¹H NMR (270 MHz) δ 9.25 (s, 1H), 8.39 (d, 1H, *J*=5.3 Hz), 7.77 (s, 1H), 7.46 (d, 1H, *J*=5.5 Hz), 5.25 (overlapping heptet, 2H), 5.07 (s, 1H), 1.46-1.32 (m, 12H); ¹³C NMR (67.5 MHz) δ 161.5 (+), 153.6 (+), 151.6 (-), 143.4 (+), 142.2 (-), 136.3 (+), 133.5 (+), 130.3 (+), 126.1 (-), 120.7 (-), 73.4 (-), 72.5 (-), 68.3 (-), 28.2 (-), 22.9 (-), 22.6 (-).

[2-(1-Hydroxy-2-(1-methylethoxy)-3-methyl-4-oxo-cyclobut-2-enylethynyl)-phenyl]-carbamic acid 1,1-dimethylethyl ester (41). Reaction of **26a** (406 mg, 1.87 mmol), *n*-BuLi (1.6 M in hexanes, 2.90 mL, 4.67 mmol), and 3-methyl-4-(1-methylethoxy)-3-cyclobutene-1,2-dione⁶⁹ (**40**) (290 mg, 1.88 mmol) in THF (30 mL total), as described for **28a** (30 min), gave after workup and chromatography (SiO₂, hexanes: EtOAc, 8:2) **41** (410 mg, 1.10 mmol, 48%) as a yellow solid and **26a** (81 mg, 0.37 mmol, 59%). ¹H NMR (270 MHz) δ 8.11 (d, 1H, *J*=8.5 Hz), 7.33 (dt, 1H, *J*=1.6, 7.5 Hz), 7.21 (br s, 1H), 6.93 (dt, 1H, *J*=7.5 and 1.0 Hz), 5.11 (heptet, 1H, *J*=6.3 Hz), 4.24 (br s, 1H), 1.71 (s, 1H), 1.53 (s, 9H), 1.49 (d, 6H,

$J=6.3$ Hz); ^{13}C NMR (67.5 MHz) δ 187.6 (+), 180.1 (+), 152.5 (+), 139.7 (+), 132.1 (-), 130.1 (-), 124.3 (+), 122.1 (-), 118.0 (-), 110.0 (+), 90.1 (+), 84.8 (+), 83.2 (+), 80.9 (+), 78.5 (-), 28.2 (-), 22.9 (-), 22.6 (-), 6.5 (-); IR (CCl_4) 3410, 2980, 2380, 1735, 1157 cm^{-1} .

E- and Z-[2-(3-(1-methylethoxy)-4-methyl-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (42). Reaction of **41** (310 mg, 0.83 mmol) in 1,2-dichloroethane (20 mL),⁷⁰ as described for **33e** (18h), gave after chromatography (SiO_2 , hexanes:EtOAc, 8:2) an inseparable mixture of **E-** and **Z-42** (152 mg, 0.41 mmol, 8.3:1 ratio, 49%) as a yellow solid. mp 132-136 °C; ^1H NMR (270 MHz) δ 8.05 (dd, 1H, $J=7.9$ and 1.6 Hz), 7.76 (d, 1H, $J=8.3$ Hz), 7.48 (s, 1H), 7.43 (dt, 1H, $J=7.7$ and 1.6 Hz), 7.16 (t, 1H), 6.63 (br s, 1H), 5.73 (heptet, 1H, $J=6.1$ Hz), 1.99 (s, 3H), 1.51 (s, 9H), 1.41 (d, 6H, $J=5.9$ Hz); ^{13}C NMR δ (150 MHz) 189.3 (+), 188.2 (+), 164.8 (+), 152.9 (+), 138.1 (+), 137.5 (+), 132.7 (-), 132.2 (-), 131.9 (-), 131.5 (-), 127.9 (+), 123.7 (-), 122.6 (-), 80.9 (+), 74.8 (-), 74.7 (-), 28.2 (-), 23.2 (-), 7.2 (-); IR (CCl_4) 3400, 2978, 2931, 2359, 1733, 1156 cm^{-1} .

2-(1-Methylethoxy)-3-methylcyclopenta[b]quinolin-1-one (43). Reaction of **42** (141 mg, 0.39 mmol) in EtOAc:HCl (3:2, 3 M aq. HCl, 25 mL), was stirred at room temperature for 3h followed by heating at 60 °C for 1h. The solvents were removed under reduced pressure and the residue was diluted in 50 mL H_2O . The aqueous phase was extracted with 3X 50 mL of Et_2O , washed with 20 mL

saturated NaHCO₃, dried (MgSO₄) and chromatographed on silica gel (hexanes:EtOAc, 8:2) gave **43** (54 mg, 0.21 mmol, 56%) as a yellow-orange solid. mp 78-80 °C; ¹H NMR (270 MHz) δ 7.94 (d, 1H, *J*=8.3 Hz), 7.93 (s, 1H), 7.71 (d, 1H, *J*=8.3 Hz), 7.63 (t, 1H, *J*=7.1 Hz), 7.39 (t, 1H, *J*=7.5 Hz), 5.28 (heptet, 1H, *J*=6.1 Hz), 2.19 (s, 3H), 1.34 (d, 6H, *J*=6.1 Hz); ¹³C NMR δ 189.4 (+), 163.9 (+), 156.1 (+), 150.1 (+), 139.0 (+), 131.3 (-), 130.5 (-), 129.6 (-), 128.1 (-), 127.5 (+), 126.6 (-), 123.3 (+), 73.9 (-), 23.2 (-), 8.3 (-); IR (CCl₄) 2988, 2254, 1707, 1636, 1102 cm⁻¹.

2-(1-methylethoxy)-3-methylcyclopenta[*b*]quinolin-1-ol (44). Reaction of **43** (90 mg, 0.36 mmol), NaBH₄ (140 mg, 3.70 mmol), and methanol (1.7 mL, 39.1 mmol) in THF (10 mL), as described for **35a** (3 h), gave after workup and chromatography (SiO₂, hexanes:EtOAc) **44** (73 mg, 0.29 mmol, 81%) as a yellow oil. Tentative NMR assignments from a rapidly decomposing compound: ¹H NMR δ 7.76 (d, 1H, *J*=8.4 Hz), 7.53 (dt, 1H, *J*=7.8 and 2.4 Hz), 7.24 (dt, 1H, *J*=8.4 and 1.8 Hz), 7.15 (dd, 1H, *J*=7.8 and 1.8 Hz), 6.99 (s, 1H), 5.01 (heptet, 1H, *J*=5.4 Hz), 4.97 (t, 1H, *J*=1.8 Hz), 1.91 (d, 3H, *J*=1.2 Hz), 1.46 (d, 3H, *J*=6.6 Hz), 1.30 (d, 3H, *J*=6.6 Hz); ¹³C NMR δ 167.3 (+), 164.7 (+), 147.7 (+), 132.1 (+), 128.8 (-), 128.3 (-), 127.5 (-), 127.4 (+), 126.3 (+), 124.1 (-), 115.8 (+), 72.7 (-), 69.6 (-), 23.3 (-), 23.1 (-), 6.9 (-).

N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide. (46)

N-(2-Ethynyl-phenyl)-acetamide⁷¹ (**45**) (330 mg, 2.07 mmol) was dissolved in 10 mL THF and cooled to -78 °C. *n*-BuLi (1.6M in pentane, 3.40 mL, 5.41 mmol) was added slowly via syringe and stirred for 15 minutes at -78 °C. The dilithiated acetanilide was then transferred via cannula to a cold (-78 °C) 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (**27**) (415 mg, 2.09 mmol) /THF (10 mL) solution and allowed to stir for 30 minutes. The reaction was then allowed to warm to room temperature over 20 minutes. The reaction was quenched with 20 mL water and 5 mL saturated NH₄Cl solution. The resulting biphasic mixture was extracted with (3 X 50 mL) diethyl ether. The organic layers were combined and washed with one portion of 30 mL saturated NaCl solution, dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes: EtOAc, 1:1) to give **46** (530 mg, 1.48 mmol, 71%) as a thick orange oil. ¹H NMR (270 MHz) δ 8.26-8.23 (m, 2H), 7.34-7.23 (m, 2H), 6.96 (t, 1H, J = 7.5 Hz), 5.96 (br. s, 1H), 5.06 (heptet, 1H, J = 6.1 Hz), 4.79 (heptet, 1H, J = 6.1 Hz), 2.23 (s, 3H), 1.46 (d, 6H, J = 5.8 Hz), ; ¹³C NMR (67.5 MHz) δ 182.2 (+), 169.3 (+), 165.1 (+), 139.3 (+), 133.6 (+), 131.7 (-), 129.9 (-), 123.2 (-), 120.1 (-), 110.9 (+), 90.4 (+), 83.9 (+), 78.4 (-), 74.2 (-), 24.5 (-), 22.6 (-), 22.4 (-). ; IR (neat) 3312 (br.), 2980, 1773, 1673 cm⁻¹.

Alternative Procedure for: N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide (46).

4-Ethynyl-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone⁶⁹ (**39**) (391 mg, 1.74 mmol), bis(triphenylphosphine)palladium dichloride (62 mg, 0.088 mmol), copper iodide (336 mg, 1.76 mmol) were slurried in 30 mL NEt₃. (**49**) (912 mg, 2.612 mmol) was added after five minutes and the reaction was allowed to stir. After 24 hours the reaction was diluted with 50 mL water and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with 20 mL 10% NH₄OH, dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes: EtOAc, 1:1) to give **46** (278 mg, 0.78 mmol, 45%) as a thick orange oil and **49** (118 mg, 0.45 mmol, 60%).

N-[2-(3,4-Diisopropoxy-2,5-dioxo-cyclopent-3-enylidenemethyl)-phenyl]-acetamide (51).

N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide (**46**) (390 mg, 1.09 mmol) was dissolved in 100 mL toluene and heated to reflux for 18 hours. The reaction was allowed to cool to room temperature and the solvent was removed. The residue was chromatographed on silica gel (hexanes:EtOAc 1:1) to give **51** (281 mg, 0.78 mmol, 72%) as an orange oil. ¹H NMR (270 MHz) δ 7.99 (br. s, 1H), 7.88 (d, 1H, J = 7.5 Hz), 7.82 (d, 1H, J = 8.1 Hz), 7.44 (t overlapping with s seen at 7.41, 1H, 7.1 Hz), 7.41 (s overlapping with t seen at 7.44, 1H), 5.54 (m, 2H), 2.22 (s, 3H), 1.36 (d, 6H, J =

6.1 Hz), 1.33 (d, 6H, J = 6.1 Hz); ^{13}C NMR (67.5 MHz) δ 186.2 (+), 184.9 (+), 169.2 (+), 150.6 (+), 149.6 (+), 137.9 (+), 132.4 (-), 131.9 (-), 131.6 (-), 125.9 (+), 125.2 (+), 124.4 (-), 124.2 (-), 75.1 (-), 74.9 (-), 24.0 (-), 22.9 (-), 22.6 (-); IR (neat) 3321, 2981, 1703, 1667 cm^{-1} .

3-(1-Acetyl-1H-indol-3-yl)-4-isopropoxy-cyclobut-3-ene-1,2-dione. (70)

N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide (**46**) (116 mg, 0.323 mmol) was dissolved in 20 mL dry 1,2-dichloroethane. $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (16 mg, 0.078 mmol) was added and the reaction was refluxed under nitrogen for 24h. The solvent was removed under reduced pressure. The residue was chromatographed on silica gel yielding **70** (69 mg, 0.233 mmol, 72%) as a red orange oil. ^1H NMR (270 MHz) δ 7.71 (d, 1H, J = 8.1 Hz), 7.53 (dt, 1H, J = 1.4, 7.5 Hz), 7.38 – 7.31 (m, 2H), 6.14 (s, 1H), 5.62 (heptet, 1H, J = 6.1 Hz), 2.43 (s, 3H), 1.51 (d, 6H, J = 6.1 Hz); ^{13}C NMR δ 191.9 (+), 191.6 (+), 191.0 (+), 172.2 (+), 157.7 (+), 154.4 (+), 140.4 (+), 133.6 (-), 128.3 (-), 126.6 (-), 123.7 (-), 118.7 (+), 86.8 (-), 78.8 (-), 23.1 (-), 20.9 (-); IR (neat) 3088, 2985, 1775, 1725, 1653, 1239 cm^{-1} .

N-[2-(2-Isopropoxy-3,4-dioxo-cyclobut-1-enylethynyl)-phenyl]-acetamide

(71). N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide (**46**) (164 mg, 0.46 mmol) was dissolved in 20 mL dry 1,2-dichloroethane. N-chlorosuccinimide (64 mg, 0.48 mmol) was added and the reaction was heated to reflux for 4 hours. After cooling to room temperature the

solvent was removed under reduced pressure. The residue was chromatographed on silica gel yielding **71** (105 mg, 0.35 mmol, 77%) as a yellow solid. mp 139-141 °C. ^1H NMR δ 8.40 (d, 1H, J = 8.4 Hz), 7.95 (br. s, 1H), 7.46 – 7.42 (m, 2H), 7.08 (t, 1H, J = 7.2 Hz), 5.43 (heptet, 1H, J = 6.0 Hz), 2.27 (s, 3H), 1.54 (d, 6H, J = 6.6 Hz); ^{13}C NMR δ 194.1 (+), 194.08 (+), 190.5 (+), 168.6 (+), 159.4 (+), 139.7 (+), 132.6 (-), 131.9 (-), 123.6 (-), 120.0 (-), 114.0 (+), 109.8 (+), 82.3 (+), 81.5 (-), 24.7 (-), 22.6 (-); IR (neat) 3325, 2991, 2191, 1784, 1766, 1676 cm^{-1} .

***tert*-butyl 2-(2-(2-isopropoxy-3,4-dioxocyclobut-1-**

enyl)ethynyl)phenylcarbamate (72). [2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (**28a**). (193 mg, 0.47 mmol) was dissolved in 20 mL dry 1,2-dichloroethane. *N*-chlorosuccinimide (71 mg, 0.53 mmol) was added and the reaction was heated to reflux for 4 hours. After cooling to room temperature the solvent was removed under reduced pressure. The residue was chromatographed on silica gel yielding **72** as an orange oil (85 mg, 0.24 mmol, 51%) ^1H NMR δ (270 MHz) 8.22 (d, 1H, J = 8.3 Hz), 7.49-7.42 (m, 2H), 7.13 (br. s, 1H), 7.04 (dt, 1H, J = 1.0, 7.5 Hz), 5.46 (heptet, 1H, J = 6.3 Hz), 1.57 (d overlapping s at 1.55, 6H, J = 6.3 Hz), 1.55 (s overlapping d at 1.57, 9H); ^{13}C NMR δ 194.7 (+), 194.5 (+), 189.9 (+), 159.9 (+), 152.0 (+), 140.1 (+), 132.4 (-), 122.5 (-), 118.2 (-), 113.9 (-), 109.1 (+), 81.8 (+), 81.4 (+), 81.1 (-), 28.6 (-), 22.6 (-). IR (neat) 3411, 2981, 2934, 2184, 1786, 1730, 1089 cm^{-1} .

4-(2-Benzylamino-phenylethynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone (48).

Benzyl-(2-ethynyl-phenyl)-amine⁷² (**47**) (410 mg, 1.98 mmol) was dissolved in THF (10 mL) *n*-BuLi (2.82 M in hexanes, 0.74 mL, 2.09 mmol) was slowly added via syringe. After 20 min, a -5°C cold solution 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (**27**) (394 mg, 1.99 mmol) in THF (10 mL) was added to the lithiated compound *via* cannula. The resulting reaction mixture was stirred (-5°C , 30 min) followed by the addition of water and saturated NH_4Cl solution (30 mL and 5 mL respectively). The biphasic mixture was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with 30 mL brine, dried (MgSO_4), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO_2 , hexanes:EtOAc, 8:2) to afford **48** (191 mg, 0.47 mmol, 24%) as a yellow brown solid. mp $134\text{--}135^{\circ}\text{C}$ and **47** (158 mg, 0.76 mmol, 39%). ^1H NMR (270 MHz) δ 7.34–7.21 (m, 5H), 7.11 (dt, 1H, $J = 1.5$ and 7.1 Hz), 6.58 (t, 1H, $J = 7.5$ Hz), 6.49 (d, 1H, $J = 8.3$ Hz), 5.24 (br. s, 1H), 4.99 (heptet, 1H, $J = 6.1$ Hz), 4.83 (heptet, 1H, $J = 5.9$ Hz), 4.43 (s, 2H), 3.71 (br. s, 1H), 1.41 (d, 3H, $J = 6.1$ Hz), 1.36 (d, 3H, $J = 6.2$ Hz), 1.27 (overlapping d, 3H, $J = 6.1$ Hz), 1.25 (overlapping d, 3H, $J = 5.9$ Hz); ^{13}C NMR δ 182.0 (+), 165.1 (+), 149.2 (+), 139.3 (+), 133.6 (+), 132.3 (–), 130.4 (–), 128.5 (–), 126.9 (–), 126.8 (–), 116.0 (–), 110.0 (–), 105.9 (+), 89.0 (+), 85.8 (+), 78.8 (+), 78.2 (–), 74.2 (–), 47.2 (+), 22.7 (–), 22.6 (–), 22.5 (–), 22.4 (–); IR (neat) 3383, 3207, 2976, 2215, 1770, 1094 cm^{-1} .

9-Benzyl-2,3-diisopropoxy-9H-carbazole-1,4-dione (69) and 2,3-diisopropoxy-1H-cyclopenta[b]quinolin-1-one (34a).

4-(2-Benzylamino-phenylethynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone (**48**) (130 mg, 0.32 mmol) was slurried along with CuI (122 mg, 0.64 mmol) in dry DMF (3 mL) and was heated to 100 °C for 3h. The reaction was cooled, diluted with 100 mL Et₂O and filtered through a small pad of Celite. The Celite was also washed with Et₂O (3 X 25 mL). The combined organic layers were washed with 200 mL brine, dried (Na₂SO₄), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 9:1) to afford **69** (16 mg, 0.039 mmol, 12%) as a yellowish oil and **34a** (quinoline) (10 mg, 0.034 mmol, 10%). NMR data for **69**. ¹H NMR δ 7.5 (d, 1H, J = 6.6 Hz), 7.37 (d, 1H, J = 7.2 Hz), 7.33-7.26 (m, 5H), 6.95 (t, 1H, J = 7.8 Hz), 6.76 (t, 1H, J = 7.2 Hz), 6.00 (d, 1H, J = 7.2 Hz), 5.50 (heptet, 1H, J = 6.6 Hz), 5.44 (heptet, 1H, J = 6.0 Hz), 5.00 (s, 2H), 1.38 (overlapping d, 6H, J = 6.0 Hz), 1.37 (overlapping d, 6H, J = 6.0 Hz); ¹³C NMR δ 186.2 (+), 185.3 (+), 159.7 (+), 155.7 (+), 149.4 (+), 148.2 (+), 136.9 (+), 131.7 (-), 130.5 (+), 128.5 (-), 128.4 (-), 127.5 (-), 124.2 (-), 122.3 (-), 106.6 (-), 105.7 (+), 74.5 (-), 74.4 (-), 54.0 (+), 23.0 (-), 22.9 (-); IR (neat) 2980, 1730, 1667, 1090 cm⁻¹.

4-(4-Benzylamino-but-1-ynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone (88).

Benzyl-but-3-ynyl-amine⁵⁸ (**83**) (783 mg, 4.92 mmol) was dissolved in 10 mL of dry THF and subsequently cooled to -40 °C. *n*-BuLi (2.0M in pentane, 2.50 mL,

5.00 mmol) was added slowly via syringe and stirred for 15 minutes at -40 °C. A cold (-40 °C) 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (**27**) (989 mg, 4.99 mmol) /THF (10 mL) solution was added to the lithiated butyne and stirred for 30 minutes at -40 °C. The reaction was quenched at -40 °C with 30 mL water. The resulting mixture was extracted with (3 X 50 mL) diethyl ether. The organic layers were combined, dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO₂, EtOAc) to give **88** (1.489 g, 4.02 mmol, 85%) as a yellow oil. ¹H NMR (270 MHz) δ 7.37 – 7.22 (m, 5H), 4.93 (overlapping heptet, 1H, J = 6.3 Hz), 4.86 (overlapping heptet, 1H, J = 6.3 Hz), 3.79 (s, 2H), 2.76 (t, 2H, J = 6.5 Hz), 2.52 (t, 2H, J = 6.5 Hz), 1.39 (d, 6H, J = 6.3 Hz), 1.29 (dd, 6H, J = 3.94, 5.94 Hz); ¹³C NMR δ 181.8 (+), 165.1 (+), 138.9 (+), 133.1 (+), 128.4 (-), 128.3 (-), 127.1 (-), 86.5 (+), 77.8 (-), 77.4 (+), 77.3 (+), 73.7 (-), 22.7 (-), 22.6 (-), 22.5 (-), 22.4 (-), 19.5 (+); IR (neat) 3293 (br.), 2231, 2060, 2978, 1772, 1623 cm⁻¹.

1-Benzyl-5,6-diisopropoxy-2,3-dihydro-1H-indole-4,7-dione (91).

4-(4-Benzylamino-but-1-ynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone (**88**) (221 mg, 0.618 mmol) was dissolved in 100 mL toluene and heated at reflux for 21 hours. The reaction was cooled to room temperature and the solvent was removed. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc 8:2 then 1:1) to give **91** (113 mg, 0.32 mmol, 51%) as a blue oil. It was noticed that during the column the residue changed in color from a slow moving yellow to faster moving green and then finally to blue. ¹H NMR (270

MHz) δ 7.32 – 7.22 (m, 5H), 5.06 (heptet, 1H, J = 6.2 Hz), 4.88 (s, 2H), 4.47 (heptet, 1H, J = 6.3 Hz), 3.55 (t, 2H, J = 10.6 Hz), 2.80 (t, 2H, J = 10.5 Hz), 1.32 (d, 6H, J = 8.3 Hz), 1.30 (d, 6H, J = 8.3 Hz); ^{13}C NMR (150 MHz) δ 180.3 (+), 177.9 (+), 149.0 (+), 148.6 (+), 136.6 (+), 128.7 (-), 128.5 (-), 127.9 (-), 127.7 (+), 112.9 (+), 76.2 (-), 75.5 (-), 52.4 (+), 51.5 (+), 23.9 (+), 22.8 (-), 22.5 (-); IR (neat) 2975, 1760, 1617 cm^{-1} .

5,6-Diisopropoxy-2,3-dihydro-1H-indole-4,7-dione (93).

1-Benzyl-5,6-diisopropoxy-2,3-dihydro-1H-indole-4,7-dione (**91**) (77 mg, 0.216 mmol) was dissolved in 10 mL methanol. Ammonium formate pentahydrate (366 mg, 2.16 mmol) and a portion of 10% Pd/C (43 mg) were added to the flask and the reaction was heated to reflux for 2 hours. The opaque dark blue solution turned clear light blue in color after about 5 minutes into the heating. The reaction was allowed to cool to room temperature and filtered through a small pad of Celite with excess methanol. The methanol was removed and the residue was diluted with 100 mL CH_2Cl_2 and washed with 50 mL of water. The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed on silica gel (hexanes:EtOAc 1:1) yielding **93** (16 mg, 0.060 mmol, 28%) as a green-blue oil. ^1H NMR δ 4.99 (heptet, 1H, J = 6.0 Hz), 4.89 (br. s, 1H), 4.48 (heptet, 1H, J = 6.9 Hz), 3.71 (t, 2H, J = 10.2 Hz), 2.93 (t, 2H, J = 10.2 Hz), 1.30 (d, 6H, J = 6.0 Hz), 1.26 (d, 6H, J = 6.0 Hz); ^{13}C NMR δ 197.6 (+), 197.5 (+), 179.0 (+), 178.8 (+), 173.6 (+), 151.8 (+), 149.7 (+), 141.9 (+), 112.3

(+), 76.4 (-), 75.5 (-), 46.8 (+), 26.5 (+), 22.8 (-), 22.5 (-); IR (neat) 3344 (br.), 2977, 1664 cm^{-1} .

1-Benzyl-5,6-diisopropoxy-1*H*-indole-4,7-dione (94).

1-Benzyl-5,6-diisopropoxy-2,3-dihydro-1*H*-indole-4,7-dione (**91**) (40 mg, 0.113 mmol) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (27 mg, 0.117 mmol) was dissolved in 5 mL benzene. The reaction was allowed to stir at room temperature for 22 hours and then was heated to reflux for 24 additional hours. The solvent was removed and the residue was chromatographed (SiO_2 , hexanes:EtOAc 8:2) yielding **94** (26 mg, 0.073 mmol, 65%) as a orange oil. ^1H NMR δ 7.34-7.24 (m, 5H), 6.84 (d, 1H, $J = 2.4$ Hz), 6.56 (d, 1H, $J = 3.0$ Hz), 5.53 (s, 2H), 4.78 (heptet, 1H, $J = 6.0$ Hz), 7.73 (heptet, 1H, $J = 6.0$ Hz), 1.32 (d, 6H, $J = 6.6$ Hz), 1.31 (d, 6H, $J = 6.0$ Hz); ^{13}C NMR δ 180.1 (+), 175.6 (+), 146.9 (+), 146.7 (+), 136.2 (+), 129.6 (-), 128.9 (-), 128.2 (-), 127.7 (-), 127.6 (+), 125.7 (+), 107.7 (-), 76.1 (-), 52.0 (+), 22.7 (-), 22.6 (-); IR (neat) 3112, 2976, 1648 cm^{-1} .

***tert*-butyl benzyl-4-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)but-3-ynylcarbamate (89).** *tert*-butyl benzylbut-3-ynylcarbamate⁵⁷ (**87**) (641 mg, 2.47 mmol) was dissolved in 5 mL THF and cooled to -78°C . The *n*-BuLi (2.0M in hexanes, 1.25 mL, 2.50 mmol) was added over a 15 min. period and allowed to stir for 30 minutes. **27** was added (5 mL) THF was added *via* cannula and allowed to stir for 30 minutes. The reaction was quenched with 30 mL and extracted with 3X 50 mL Et_2O , dried (MgSO_4), filtered and concentrated. The

residue was chromatographed on silica gel (hexanes:EtOAc 8:2) yielding **89** as a thick yellow oil (704 mg, 1.54 mmol, 62%). ^1H NMR δ (270 MHz) 7.31-7.16 (m, 5H), 4.97 (heptet, 1H, J = 6.2 Hz), 4.84 (heptet, 1H, J = 6.2 Hz), 4.51 (s, 2H), 4.30 (br. d, 1H, J = 11.1 Hz), 3.38 (br. s, 1H), 3.26 (br. s, 1H), 2.45 (br. s, 2H), 1.41 (s overlapping with d at 1.40, 9H), 1.40 (d overlapping with s at 1.41, 6H, J = 6.3 Hz), 1.26 (d, 6H, J = 5.2 Hz). ^{13}C NMR δ (67.5 MHz) 181.1 (+), 164.9 (+), 155.3 (+), 138.1 (+), 137.9 (+), 133.3 (+), 128.2 (-), 127.6 (-), 126.9 (-), 86.9 (+), 86.2 (+), 79.9 (-), 78.2 (-), 77.5 (-), 77.4 (+), 76.2 (-), 73.6 (+), 51.2 (-), 50.3 (-), 45.4 (-), 45.1 (-), 30.7 (+), 28.2 (+), 22.5 (+), 22.4 (+), 22.3 (+), 18.7 (-), 18.5 (-). IR (neat) 3340 br., 2990, 2930, 2106, 1767, 1686, 1094 cm^{-1} .

***tert*-butyl benzyl-2-(4,5-diisopropoxy-3,6-dioxocyclohexa-1,4-dienyl)ethylcarbamate (92).** *tert*-butyl benzyl-4-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)but-3-ynylcarbamate (**89**) (560 mg, 1.22 mmol) was dissolved in 20 mL 1,2-DCE and placed in a thick walled flask. The flask was sealed and heated to 100 $^{\circ}\text{C}$ for 22h. The reaction was cooled to room temperature and solvents were removed. The resulting residue was chromatographed on silica gel (hexanes:EtOAc; 8:2) yielding **92** as an orange oil (266 mg, 0.58 mmol, 48%) ^1H NMR (270 MHz) δ 7.40-7.23 (m, 5H), 6.26 (s, 1H), 4.79 (heptet, 2H, J = 5.8 Hz), 4.45, (s, 2H), 3.40 (br. s, 2H), 2.54 (t, 2H, J = 6.7 Hz), 1.43-1.27 (m, 21H). ^{13}C NMR δ 184.3 (+), 155.6 (+), 145.3 (+), 131.3 (+), 128.5 (+), 128.3 (-), 128.1 (-), 127.3 (-), 80.0 (+), 76.0 (+), 75.9 (+), 50.8 (+), 45.5 (+), 28.6 (-), 28.3 (-), 28.1 (-), 22.9 (-), 22.7 (-), 22.6 (-). IR (neat) 2977, 2933, 1686, 1654, 1095 cm^{-1} .

1-Benzyl-5,6-diisopropoxy-2,3-dihydro-1H-indole-4,7-dione (91). *tert*-butyl benzyl2-(4,5-diisopropoxy-3,6-dioxocyclohexa-1,4-dienyl)ethylcarbamate (**92**) (200 mg, 0.44 mmol) was dissolved in CH₂Cl₂ (20 mL) was treated with 1.5 mL trifluoroacetic acid⁷³ at 0 °C for 3h. The reaction was then warmed to 50 °C for 1h. The reaction was cooled to room temperature and the solvents were removed under reduced pressure. The resulting residue was neutralized with 30 mL aqueous saturated NaHCO₃ and extracted with 3X 30 mL portions of CH₂Cl₂. The organic layer was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes:EtOAc, 8:2) to give **91** (80 mg, 0.22 mmol, 51%) as a blue oil.

[2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (33a). A solution of **28a** (184 mg, 0.44 mmol) in N,N-dimethylformamide (DMF) (3 mL) was heated to 100 °C for 6h. The reaction was cooled to ambient temperature, diluted with 100 mL Et₂O and filtered through a pad of Celite and rinsed with 2X 25 mL Et₂O. The organic washings were combined and washed with 20 mL brine, dried (Na₂SO₄) and concentrated. The solvent was then removed under reduced pressure and the residue was purified by chromatography (SiO₂, hexanes: EtOAc, 8:2) to give **33a** (19 mg, 0.048 mmol, 11%) as an orange solid. mp 93-96 °C; ¹H NMR (270 MHz) δ 7.91 (dd, 1H, *J*=7.9 and 1.6 Hz), 7.80 (d, 1H, *J*=8.1 Hz), 7.44 (s, 1H),

overlapping 7.40 (t, 1H, $J=8.7$ Hz), 7.13 (t, 1H, $J=7.5$ Hz), 6.54 (br s, 1H), 5.59 (m, 2H), 1.51 (s, 9H), 1.40 (d, 6H, $J=6.3$ Hz), 1.37 (d, 6H, $J=6.1$ Hz).

This reaction was also repeated in several different temperatures and times and are summarized in Table 5.

Table 5: Copper Mediated Reaction Conditions for 28a

Temp/Time/28a	CuI	33a	Recovered 28a
75 °C, 24h, 28a 120 mg, 0.29 mmol	Yes 2 eq	No Reaction	Not Calculated
85 °C, 24h, 28a (120 mg, 0.29 mmol)	Yes 2 eq	10 mg, 0.024 mmol, 8%	29 mg, 0.069 mmol, 24%
100 °C, 6h, 28a 184 mg, 0.44 mmol	Yes 2 eq	19 mg, 0.048 mmol, 11%	Not recovered
120 °C, 1h, 28a 212 mg, 0.51 mmol	Yes 2 eq	24 mg, 0.057 mmol, 11%	70 mg, 0.17 mmol, 32%
120 °C, 1h, 28a 166 mg, 0.40 mmol	No	38 mg, 0.091 mmol, 23%	13 mg, 0.032 mmol, 8%)

4-hydroxy-2,3-diisopropoxy-4-(2-(2-nitrophenyl)ethynyl)cyclobut-2-enone

(51a). 4-Ethynyl-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone⁶⁹ **39** (370 mg, 1.65 mmol), bis(triphenylphosphine)palladium dichloride (56 mg, 0.080 mmol), copper iodide (317 mg, 1.66 mmol) were slurried in 30 mL NEt₃.

Iodonitrobenzene (418 mg, 1.68 mmol) was added after five minutes and the reaction was allowed to stir. After 24 hours the reaction was diluted with 50 mL water and extracted with diethyl ether (3 x 50 mL). The combined organic layers

were washed with 20 mL 10% NH₄OH, dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (SiO₂, hexanes: EtOAc, 1:1) to give **51a** (300 mg, 0.57 mmol, 53%) as a yellow oil ¹H NMR (270 MHz) δ 8.07 (dd, 1H, J = 1.8, 8.3 Hz), 7.66 (dd, 1H, J = 1.8, 7.9 Hz), 7.59 (dt, 1H, J = 1.1, 7.5 Hz), 7.49 (dt, 1H, J = 1.6, 8.1 Hz), 5.06 (heptet, 1H, J = 6.1 Hz), 4.91 (heptet, 1H, J = 6.1 Hz), 3.03 (br. s, 1H), 1.47 (d, 6H, J = 6.1 Hz), 1.34-1.31 (overlapping d, 6H, J = 6.2, 6.1 Hz). ¹³C NMR (67.5 MHz) δ 179.6 (+), 163.9 (+), 149.4 (+), 135.0 (-), 134.2 (+), 132.9 (-), 129.3 (-), 124.6 (-), 117.3 (+), 91.3 (+), 83.7 (+), 79.1 (+), 78.4 (-), 74.3 (-), 22.6 (-), 22.5 (-). IR (neat) 3348 br., 2980, 2934, 2368, 1774, 1609, 1319 cm⁻¹.

2-(2-nitrobenzylidene)-4,5-diisopropoxycyclopent-4-ene-1,3-dione (51d) and 2,3-diisopropoxy-5-(2-nitrophenyl)cyclohexa-2,5-diene-1,4-dione (51c). 4-hydroxy-2,3-diisopropoxy-4-(2-(2-nitrophenyl)ethynyl)cyclobut-2-enone **51a** was dissolved in 200 mL toluene and heated to reflux for 5 hours. The reaction was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was chromatographed (SiO₂, hexanes:EtOAc, 8:2) yielding **51c** (141 mg, 0.41 mmol, 33%) as a brown oil and **51d** (47 mg, 0.14 mmol, 11%) Data for **51c** ¹H NMR δ 8.15 (dd, 1H, J = 1.2, 8.4 Hz), 7.70 (s, 1H), 7.68 (dd, 1H, J = 1.2, 7.2 Hz), 7.64 (dt, 1H, J = 1.2, 7.2 Hz), 7.56 (dt, 1H, J = 1.2, 6.0 Hz), 5.64 (heptet, 1H, J = 6.0 Hz), 4.95 (heptet, 1H, J = 6.0 Hz), 1.41 (d, 6H, J = 6.0 Hz), 1.35 (d, 6H, J = 6.0 Hz). ¹³C NMR δ 184.7 (+), 183.8 (+), 152.5 (+), 150.7 (+), 148.1 (+), 132.8 (-), 132.5 (-), 131.2 (-), 130.2 (+), 129.1 (+), 128.3 (+),

124.6 (-), 75.2 (-), 75.1 (-), 23.1 (-), 22.9 (-). IR (neat) 2990, 1732, 1673, 1655, 1340 cm^{-1} . Data for **51d** ^1H NMR δ 7.72-7.58 (br. d, 2H), 7.24 (d overlapping CHCl_3 , 1H), 7.10 (t, 1H, $J = 7.3$ Hz), 6.47 (s, 1H), 5.51 (overlapping heptets, 2H, $J = 6.1$), 1.41 (d overlapping d at 1.38, 6H, $J = 7.1$ Hz), 1.38 (d overlapping d at 1.41, 6H, $J = 6.5$ Hz)

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Appendix

Figure 4: ¹H Spectrum of (4-Chloro-2-iodophenyl)-carbamic acid 1,1-dimethylethyl ester **37b**

Figure 5: ^{13}C Spectrum of (4-Chloro-2-iodophenyl)-carbamic acid 1,1-dimethylethyl ester **37b**

Figure 6: ^1H Spectrum of (2-Iodo-5-methoxy-phenyl)-carbamic acid 1,1-dimethylethyl ester **37c**

Figure 7: ^{13}C Spectrum of (2-Iodo-5-methoxy-phenyl)-carbamic acid 1,1-dimethylethyl ester **37c**

Figure 8: ^1H Spectrum of (2-Iodo-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester **37d**

Figure 9: ^{13}C Spectrum of (2-Iodo-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester **37d**

Figure 10: ¹H Spectrum of (4-Chloro-2-(trimethylsilylethynyl)phenyl)-carbamic acid 1,1-dimethylethyl ester **38b**

Figure 11: ^{13}C Spectrum of (4-Chloro-2-(trimethylsilyl)ethynyl)phenyl)-carbamic acid 1,1-dimethylethyl ester **38b**

Figure 13: ^{13}C Spectrum of (5-Methoxy-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester **38c**

Figure 14: ^1H Spectrum of (5-Methyl-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester **38d**

Figure 15: ^{13}C Spectrum of (5-Methyl-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester **38d**

Figure 16: ^1H Spectrum of (4-trimethylsilylethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester **38e**

Figure 17: ^{13}C Spectrum of (4-trimethylsilyl-1-ethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester **38e**

Figure 18: ^1H Spectrum of (4-Chloro-2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester **26b**

Figure 19: ^{13}C Spectrum of (4-Chloro-2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester **26b**

Figure 20: ^1H Spectrum of (2-Ethynyl-5-methoxyphenyl)-carbamic acid 1,1-dimethylethyl ester **26c**

Figure 21: ¹³C Spectrum of (2-Ethynyl-5-methoxyphenyl)-carbamic acid 1,1-dimethylethyl ester **26c**

Figure 22: ^1H Spectrum of (2-Ethynyl-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester **26d**

Figure 23: ^{13}C Spectrum of (2-Ethynyl-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester **26d**

Figure 24: ^1H Spectrum of (4-Ethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester **26e**

Figure 25: ^{13}C Spectrum of (4-Ethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester **26e**

Figure 26: ^1H Spectrum of [2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxocyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester **28a**

Figure 27: ^{13}C Spectrum of [2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxocyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester **28a**

Figure 28: ^1H Spectrum of [4-Chloro-2-(1-hydroxy-2,3-di(1-methylethoxy)-4-oxocyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester **28b**

Figure 29: ^{13}C Spectrum of [4-Chloro-2-(1-hydroxy-2,3-di(1-methylethoxy)-4-oxocyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester **28b**

Figure 30: ^1H Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester **28c** and butyl addition product of diisopropyl squarate

Figure 31: ^{13}C Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester **28c** and butyl addition product of diisopropyl squarate

Figure 32: ^1H Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester **28c**

Figure 33: ^{13}C Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl]-carbamic acid 1,1-dimethylethyl ester **28c**

Figure 34: ^1H Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methylphenyl]-carbamic acid 1,1-dimethylethyl ester **28d**

Figure 35: ^{13}C Spectrum of [2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methylphenyl]-carbamic acid 1,1-dimethylethyl ester **28d**

Figure 36: ^1H Spectrum of [4-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-pyridin-3-yl]-carbamic acid 1,1-dimethylethyl ester **28e**

Figure 37: ^{13}C Spectrum of [4-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-pyridin-3-yl]-carbamic acid 1,1-dimethylethyl ester **28e**

Figure 38: ¹H Spectrum of [2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester **33a**

Figure 39: ^{13}C Spectrum of [2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester **33a**

Figure 40: ^1H Spectrum of [4-Chloro-2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester **33b**

Figure 42: ^1H Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-5-methoxy-phenyl]-carbamic acid 1,1-dimethylethyl ester **33c**

Figure 44: ^1H Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-methylidene)-5-methyl-phenyl]-carbamic acid 1,1-dimethylethyl ester **33d**

Figure 45: ^{13}C Spectrum of [2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-methyldene)-5-methyl-phenyl]-carbamic acid 1,1-dimethylethyl ester **33d**

STANDARD PROTON PARAMETERS									
exp2 sz2pu1					SPECIAL				
date	Oct 16 2013	temp	25.0						
date ent	Oct 16 2013	gain	not used						
file	REPORT/EXP2	ph	22						
bjorn/vnmr50/EXP2		ph	8.008						
ps2-93-177id		ph	8.008						
ACQUISITION		attn	8.588						
sw	9584.6	flaos							
at	1.092	11							
np	3638	in							
fb	5080	dp							
g	32	ns							
o1	1.080								
ct	8	fn							
ct	8								
th TRANSMITTER		display							
strg	589.671	h1	1178.2						
tof	599.5	rfp	1178.2						
tpwr	55	rfp	150.9						
pv	4.580	lp	-23.0						
DECOUPLER		plot							
dn	c13	wc	215						
dot	8	sc	35						
dm	mnv	sc	182						
dpr	4	cs	3						
der	35888	nm	cdc						
		ph

Figure 46: ^1H Spectrum of [4-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-3-pyridinyl]-carbamic acid 1,1-dimethylethyl ester **33e**

Figure 47: ^{13}C Spectrum of [4-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-3-pyridinyl]-carbamic acid 1,1-dimethylethyl ester **33e**

Figure 48: ^1H Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[*b*]quinolin-1-one 34a

Figure 49: ^{13}C Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[*b*]quinolin-1-one 34a

Figure 50: ^1H Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[*b*]quinolin-1-one **34b**

Figure 51: ^{13}C Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[*b*]quinolin-1-one **34b**

Figure 52: ^1H Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[b]quinolin-1-one **34c**

Figure 53: ^{13}C Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[*b*]quinolin-1-one **34c**

Figure 54: ^1H Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[*b*]quinolin-1-one **34d**

Figure 55: ^{13}C Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[*b*]quinolin-1-one **34d**

Figure 56: ¹H Spectrum of 2,3-Di(1-methylethoxy)-6-aza-cyclopenta[b]quinolin-1-one **34e**

Figure 57: ^{13}C Spectrum of 2,3-Di(1-methylethoxy)-6-aza-cyclopenta[*b*]quinolin-1-one **34e**

Figure 59: ¹³C Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-ol **35a**

Figure 61: ^{13}C Spectrum of 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[b]quinolin-1-ol **35b**

Figure 62: ^1H Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[b]quinolin-1-ol **35c**

Figure 63: ^{13}C Spectrum of 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[*b*]quinolin-1-ol **35c**

Figure 64: ^1H Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[*b*]quinolin-1-ol **35d**

Figure 65: ^{13}C Spectrum of 2,3-Di(1-methylethoxy)-6-methylcyclopenta[*b*]quinolin-1-ol **35d**

Figure 66: ^1H Spectrum of 2,3-Di(1-methylethoxy)-6-azacyclopenta[*b*]quinolin-1-ol **35e**

Figure 67: ¹³C Spectrum of 2,3-Di(1-methylethoxy)-6-azacyclopenta[b]quinolin-1-ol **35e**

Figure 68: ¹H Spectrum of [2-(1-Hydroxy-2-(1-methylethoxy)-3-methyl-4-oxo-cyclobut-2-enylethynyl)-phenyl]-carbamic acid 1,1-dimethylethyl ester **41**

Figure 69: ^{13}C Spectrum of [2-(1-Hydroxy-2-(1-methylethoxy)-3-methyl-4-oxo-cyclobut-2-enylethynyl)-phenyl]-carbamic acid 1,1-dimethylethyl ester **41**

Figure 70: ^1H Spectrum of E- and Z-[2-(3-(1-methylethoxy)-4-methyl-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester **42**

Figure 71: ^{13}C Spectrum of E- and Z-[2-(3-(1-methylethoxy)-4-methyl-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl]-carbamic acid 1,1-dimethylethyl ester **42**

Figure 72: ^1H Spectrum of 2-(1-Methylethoxy)-3-methylcyclopenta[*b*]quinolin-1-one **43**

Figure 73: ¹³C Spectrum of 2-(1-Methylethoxy)-3-methylcyclopenta[b]quinolin-1-one 43

Figure 74: ¹H Spectrum of 2-(1-methylethoxy)-3-methylcyclopenta[*b*]quinolin-1-ol
44

Figure 76: ^1H Spectrum of N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide. **46**

Figure 77: ^{13}C Spectrum of N-[2-(1-Hydroxy-2,3-diisopropoxy-4-oxo-cyclobut-2-enylethynyl)-phenyl]-acetamide **46**

Figure 78: ^1H Spectrum of N-[2-(3,4-Diisopropoxy-2,5-dioxo-cyclopent-3-enyldenemethyl)-phenyl]-acetamide **51**

Figure 79: ^{13}C Spectrum of N-[2-(3,4-Diisopropoxy-2,5-dioxo-cyclopent-3-enylidenemethyl)-phenyl]-acetamide **51**

Figure 80: ^1H Spectrum of 3-(1-Acetyl-1H-indol-3-yl)-4-isopropoxy-cyclobut-3-ene-1,2-dione. **70**

Figure 81: ¹³C Spectrum of 3-(1-Acetyl-1H-indol-3-yl)-4-isopropoxy-cyclobut-3-ene-1,2-dione. **70**

Figure 82: ^1H Spectrum of N-[2-(2-Isopropoxy-3,4-dioxo-cyclobut-1-enylethynyl)-phenyl]-acetamide **71**

Figure 83: ^{13}C Spectrum of N-[2-(2-Isopropoxy-3,4-dioxo-cyclobut-1-enylethynyl)-phenyl]-acetamide **71**

Figure 84: ^1H Spectrum of *tert*-butyl 2-(2-(2-isopropoxy-3,4-dioxocyclobut-1-enyl)ethynyl)phenylcarbamate **72**

Figure 85: ¹³C Spectrum of *tert*-butyl 2-(2-(2-isopropoxy-3,4-dioxocyclobut-1-enyl)ethynyl)phenylcarbamate **72**

Figure 86: ¹H Spectrum of 4-(2-Benzylamino-phenylethynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone **48**

Figure 88: ^1H Spectrum of 9-Benzyl-2,3-diisopropoxy-9H-carbazole-1,4-dione **69**

Figure 89: ¹³C Spectrum of 9-Benzyl-2,3-diisopropoxy-9H-carbazole-1,4-dione **69**

Figure 90: ¹H Spectrum of 4-(4-Benzylamino-but-1-ynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone **88**

Figure 91: ^{13}C Spectrum of 4-(4-Benzylamino-but-1-ynyl)-4-hydroxy-2,3-diisopropoxy-cyclobut-2-enone **88**

Figure 92: ^1H Spectrum of 1-Benzyl-5,6-diisopropoxy-2,3-dihydro-1H-indole-4,7-dione **91**

Figure 93: ^{13}C Spectrum of 1-Benzyl-5,6-diisopropoxy-2,3-dihydro-1H-indole-4,7-dione **91**

93

CC(C)OC1=C(C(=O)N2CCCC2)C(=O)C(=C1)OC(C)C

Figure 95: ¹³C Spectrum of 5,6-Diisopropoxy-2,3-dihydro-1H-indole-4,7-dione **93**

Figure 96: ^1H Spectrum of 1-Benzyl-5,6-diisopropoxy-1*H*-indole-4,7-dione **94**

Figure 97: ¹³C Spectrum of 1-Benzyl-5,6-diisopropoxy-1*H*-indole-4,7-dione **94**

Figure 98: ^1H Spectrum of *tert*-butyl benzyl-4-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)but-3-ynylcarbamate **89**

Figure 99: ^{13}C Spectrum of *tert*-butyl benzyl-4-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)but-3-ynylcarbamate **89**

Figure 100: ^1H Spectrum of *tert*-butyl benzyl-2-(4,5-diisopropoxy-3,6-dioxocyclohexa-1,4-dienyl)ethylcarbamate **92**

Figure 102: ^1H Spectrum of 4-hydroxy-2,3-diisopropoxy-4-(2-(2-nitrophenyl)ethynyl)cyclobut-2-enone **51a**

Figure 103: ^{13}C Spectrum of 4-hydroxy-2,3-diisopropoxy-4-(2-(2-nitrophenyl)ethynyl)cyclobut-2-enone **51a**

S79-2

Figure 104: ¹H Spectrum of 2-(2-nitrobenzylidene)-4,5-diisopropoxycyclopent-4-ene-1,3-dione **51d**

Page 74400

Figure 105: ¹³C Spectrum of 2-(2-nitrobenzylidene)-4,5-diisopropoxycyclopent-4-ene-1,3-dione **51d**

Figure 106: ^1H Spectrum of 2,3-diisopropoxy-5-(2-nitrophenyl)cyclohexa-2,5-diene-1,4-dione **51c**

Figure 107: Expanded view of gHMBC Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[*b*]quinolin-1-ol **35a**

Figure 108: Expanded view of gHMQC Spectrum of 2,3-Di(1-methylethoxy)cyclopenta[*b*]quinolin-1-ol **35a**